

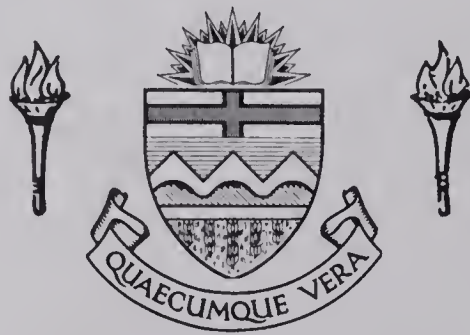
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SCHEDULE-CONTROL OF BEHAVIOR IN
THE SQUIRREL MONKEY: EFFECTS
OF METHYLPHENIDATE AND RESERPINE

by



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A DISSERTATION
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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a dissertation entitled "Schedule-Control of Behavior in the Squirrel Monkey: Effects of Methylphenidate and Reserpine," submitted by Nicholas F. Skinner in partial fulfillment of the requirements for the degree of Master of Science.

ABSTRACT

Squirrel monkeys were trained on fixed-ratio or fixed-interval schedules of reinforcement involving termination of conditioned aversive stimulation. The behaviors generated resembled in all major characteristics, patterns of responding customarily engendered by these schedules when food presentation is employed.

Drug-behavior interaction effects were investigated, with the following results:

(i) methylphenidate, a psychomotor stimulant, increased low rates of responding but decreased higher response rates; more specifically, the drug at several dosage levels exerted more pronounced effects on behavior maintained by the fixed-interval as compared with the fixed-ratio schedule of reinforcement.

(ii) reserpine, administered daily to animals working under the fixed-interval condition, caused a progressive, overall reduction in behavioral output.

(iii) methylphenidate attenuated the rate-decreasing effects of reserpine. The interactive effect of the two drugs, rather than being one of mutual neutralization, consisted of an increase in behavior in the reserpinized animals greater than that produced by methylphenidate alone at equivalent dosages.

The behavioral and pharmacological results obtained support and extend the hypothesis that the schedule per se may be a more important determinant of drug-behavior dependencies than the nature of the reinforcer used in behavioral control.

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INTRODUCTION

I

Although most current behavioral experiments with nonhuman primates use operant conditioning procedures as described by Skinner (1938), only experiments with certain additional characteristics are consistently referred to as operant conditioning experiments in current psychological terminology (Ferster, 1953). The operant conditioning experiments to be described in this thesis have these additional characteristics. The first characteristic is the extensive use of rate and pattern of responding as dependent variables. In operant conditioning experiments some response that the organism can repeat readily is usually selected for study. Such responses provide the investigator with a potentially wide range of response rates and response patterns that can be studied as a function of changes in independent variables. The second characteristic is the explicit use of schedules of reinforcement. A schedule of reinforcement is a precise specification of the plan according to which discriminative and reinforcing stimuli will be presented. The use of different schedules of reinforcement gives the investigator extremely powerful control over a variety of rates and patterns of responding.

Because of the ease with which the responses studied in operant conditioning experiments may be automatically recorded, the experimenter seeks reliable programming equipment which will allow a sophisticated yet economical arrangement of precisely scheduled reinforcement contingencies. The use of automatic electrical programming and recording equipment, though sometimes wrongly assumed to be a distinguishing characteristic of operant conditioning experiments, has been responsible

for the recent unexpected but great impact of behavioral psychology on pharmacology. In the words of P. B. Dews (1964):

. . . automatic programming led to the discovery of the importance of schedules of reinforcement. The schedule of reinforcement has a large and often decisive influence on how behavior is modified by a drug. Such a contribution to the solution of the old problem as to why the behavioral effect of a drug varies so much according to the circumstances under which it is given could not be ignored by pharmacologists.

Prior to the discovery of the importance of reinforcement scheduling, the selective effects of drugs on behavior had been explained in terms of motivational antecedents, but in recent years this has been shown to be unsatisfactory. It is a well-known fact of behavioral pharmacology that enough of any drug will abolish all behavior, no matter how maintained, by raising the level of toxicity of the drug to the level at which the dosage becomes lethal, killing the animal. Thus, that the behavior maintained by food or water or "fear" can be abolished by any given drug is not sufficient grounds for inferring that the effects of the drug are related to the motivation used in the experiments. For the drug effect to be related to an effect on motivation it is necessary that behavior dependent on one so-called motivation be shown to be affected exclusively or, at least, very preferentially. It has proved surprisingly difficult, says Dews, to achieve this result.

Most effects of drugs do not, in fact, seem to be importantly related to motivation. Moreover, what at first sight appears to be a straightforward experimental design for comparison of the effects of drugs on motivation usually turns out to be a difficult and long-term affair because of the difficulty in matching schedules of performance under different motivations. There are many claims in the literature of a selective effect of drugs, but almost all of them are based on experiments in which changes in motivational determinants are confounded with changes in procedure of a kind that is known to change sensitivity to drugs.

In essence, therefore, the nature of motivation is not generally a major determinant of the effects of drugs on behavior, and there is more talk today about schedules of reinforcement than there is of motivation.

Before discussing the manner in which schedules of reinforcement influence the behavioral effects of a given drug, it is first necessary to define the word "schedule" as it is used in operant psychology today. A great deal of behavior can be said to be maintained by its relation to reinforcing stimuli. Obviously, therefore, reinforcing stimuli and the behaviors they strengthen go together (like force and mass in physics), and once types of behavior and appropriate reinforcing stimuli are discovered *to be related*, one has systems with which to work. When stimuli have been established as reinforcing, they can be used to influence behavior by relating occurrences of the stimuli in some way to occurrences of some behavior or preceding stimuli. This "relating in some way" is called the "scheduling". A schedule, then, specifies the sequence of stimuli presented and the temporal and behavioral requirements for occurrence of the reinforcing stimuli.

The influence of schedules in determining the behavioral effects of drugs is best illustrated by an example. Kelleher and Morse used two groups of monkeys with two schedules imposed on each group, so that in total four situations were under study. In one situation, each time a response was made after a certain stimulus had been present for ten minutes, food was presented. In the second situation, in the same session for the same monkey, in the presence of a distinctive stimulus different from that prevailing under the first situation, food was presented when the thirtieth response was made. In a third situation, with the second

group of monkeys, a stimulus was removed at a response each time the stimulus had been present ten minutes. If the stimulus was allowed to persist one second longer than ten minutes, electric shocks were delivered. Finally, in the same sessions but in the presence of another stimulus, the stimulus was removed upon emission of thirty responses; persistence of the stimulus for thirty seconds precipitated shock delivery. The monkeys obtained all the food presentations and avoided all but a small proportion of the shocks.

The salient results were that: (1) the two different schedules engendered very different patterns of behavior, but the patterns were quite similar for each of the schedules whether related to food or electric shock; (2) the susceptibility of the behavior to modification by the drugs studied was also very much better related to the schedule than the reinforcer--the behavior according to the two schedules showed different susceptibility to the drugs, but behavior in the two groups of monkeys on the similar schedule had similar susceptibility. In other words, the differential effects of the drugs were according to the schedule and not the reinforcer. The authors concluded that

. . . if this sort of finding proves to be generally true, and behavior of avoidance of painful events is not specifically different from behavior for positive reinforcement in its relation to drugs, the whole speculative picture of effects of drugs on 'fear' and 'anxiety' becomes blurred, and may even be erased.

On the basis of the foregoing discussion it may justifiably be said that perhaps the most important attribute of reinforcers as a class of events lies in the vast differences in behavior which may be generated by subtle differences in reinforcement scheduling. Cognizance

of this fact was the genesis of Ferster and Skinner's monumental treatise Schedules of Reinforcement (1957), in which a schedule of reinforcement is defined not in terms of its effects on behavior, but in terms of (a) the time elapsed since the preceding reinforcement, or (b) the number of responses required of the organism for it to obtain a reinforcement. Thus four basic schedules are possible--fixed ratio, variable ratio, fixed interval, and variable interval.

Of these, two are centrally involved in the present study:

(1) fixed ratio (FR): A response is reinforced upon completion of a fixed number of responses counted from the preceding reinforcement.

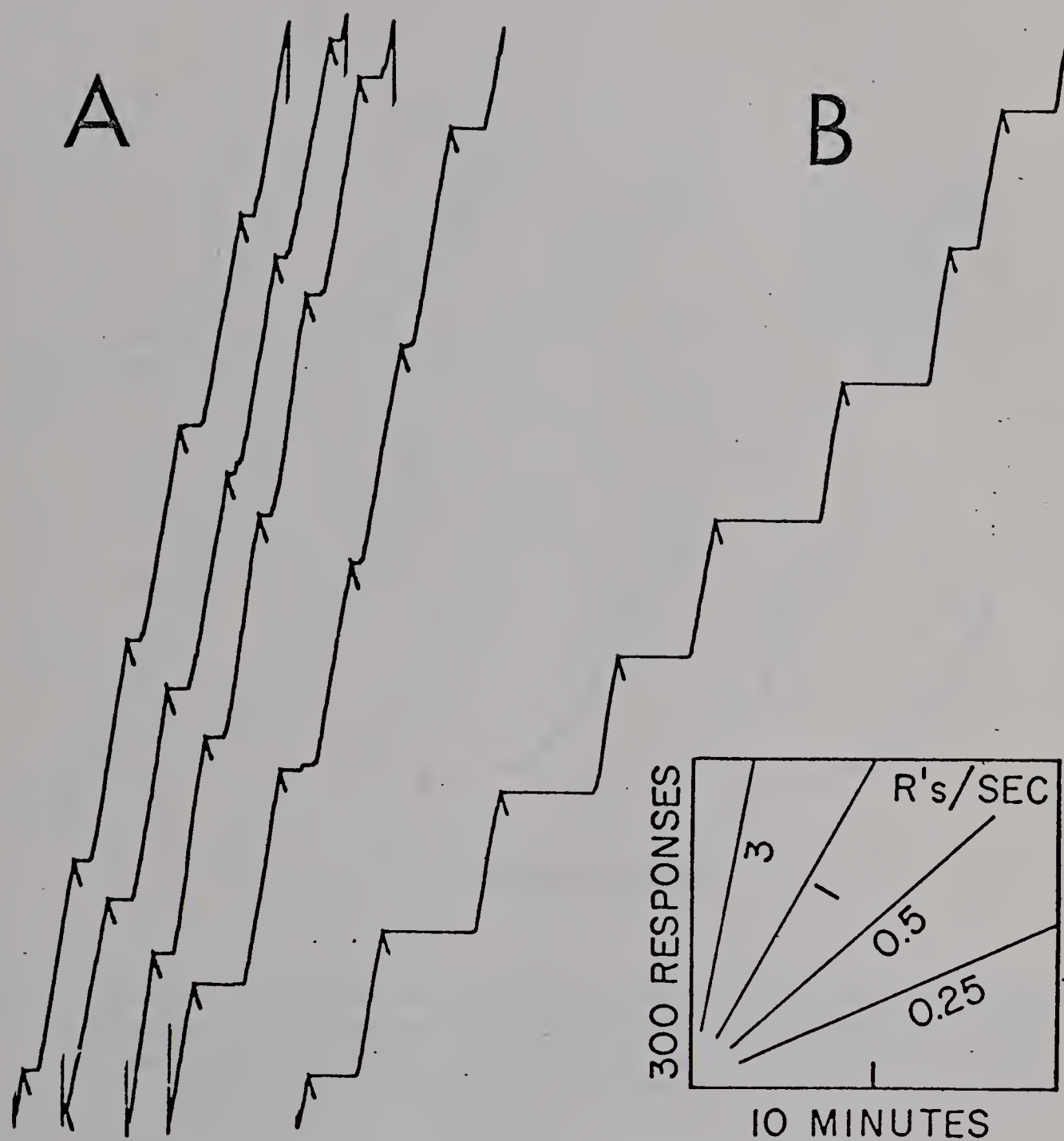
(2) fixed interval (FI): The first response after a given time interval has elapsed is reinforced.

Ferster and Skinner have exhaustively characterized both these simple schedules (see Figures 1 and 2).

From Figure 1 it is apparent that the cumulative record between any two consecutive reinforcements on an FR schedule comprises two characteristic segments: (1) a pause following reinforcement (post-reinforcement pause or PRP), and (2) a period of relatively constant, high-rate responding that continues until a reinforcement is obtained.

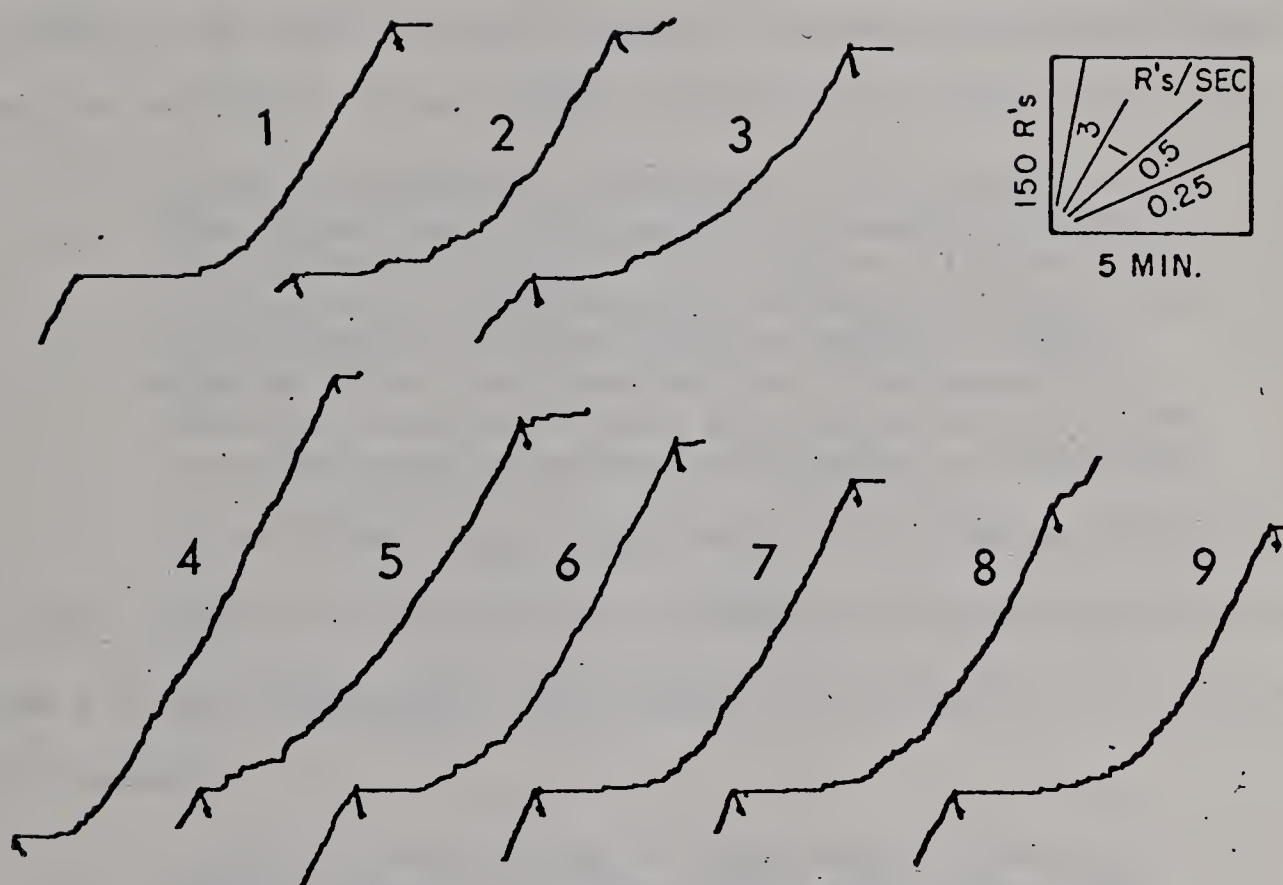
Figure 2 shows the characteristics of FI behavior to be two in number: (1) a post-reinforcement pause, followed by (2) a period of responding at a low but gradually accelerating rate.

It is the existence of such characteristic segments of schedule-controlled behaviors that is of interest to behavioral scientists, the rationale being that these segments may be differentially sensitive to drug action. Operant methodology, as characterized above, because of



Final performance on FR 200 and FR 120

Fig. 1: Cumulative records showing the characteristic behavior pattern generated by Fixed-Ratio schedules of reinforcement. The short downward strokes of the recording pen indicate delivery of reinforcement. (Ferster & Skinner, 1957, Fig. 24, p. 52)



FI 8: collected segments

Fig. 2: Cumulative records showing the characteristic behavior pattern generated by Fixed-Interval schedules of reinforcement. The short downward strokes of the recording pen indicate delivery of reinforcement. (Ferster & Skinner, 1957, Fig. 156, p. 162)

its emphases on (a) detailed observation and experimental control of individual subjects and (b) careful establishment of baseline behavior which results in a high degree of intra-subject constancy, furnishes a sound basis against which the effects of a variety of drugs and dosage levels on the characteristic segments of schedule-controlled behaviors may be evaluated. Boren (1966) puts the point succinctly:

If the experimenter is successful, each subject will behave predictably from session to session and even from minute to minute. Thus, when an effective drug is injected in the middle of a session a change from the dependable baseline behavior should be readily apparent in an individual subject. Furthermore, on different sessions, a range of dosages can be studied in the same subject with a sound basis for comparison.

In the light of such a statement, it becomes apparent that the recent application of operant methodology to pharmacological techniques was a logical development having inherent advantages for both disciplines. For example,

A drug can occasionally be found which either has a specific effect or at least has a main effect that is not seriously disrupted by secondary effects. This drug can then be used as an analytical tool. For example, Dews (1955) showed that behavior maintained by a fixed-interval (FI) schedule of reinforcement was much more sensitive to pentobarbital than was behavior maintained by a fixed-ratio (FR) schedule. In a related study, Herrnstein and Morse (1956) examined the effect of the same drug with similar values on a tandem FI FR schedule, where the behaviors generated by the two components of the schedule were joined in a single performance and could not be easily disentangled. However when pentobarbital was given at a high dosage, the post-reinforcement pause characteristic of fixed-ratio behavior remained. Thus, the drug experimentally separated the two behaviors and gave the experimenters additional evidence that the complex tandem performance could indeed be properly analyzed into simple components.

(Boren, 1966)

Thus the major theme in the orientation of this thesis consists of an examination of the research possibilities inherent in psychopharmacological manipulation of two specific schedule-generated behaviors.

II

A distinction too often overlooked in operant experiments involving negative reinforcement (e.g., removal of conditioned aversive stimulation--CAS) is the difference between "avoidance" behavior and "escape" behavior. Avoidance behavior, as defined by Dews and Morse (1961), is

. . . behavior that occurs in the presence of originally neutral stimuli, correlated in the past with a succeeding aversive stimulus, such behavior having as its consequence the prevention or postponement of the aversive stimulus. Escape behavior is behavior that occurs in the presence of aversive stimulation and that leads to cessation of that stimulation.

Azrin, Holz and Hake (1962) trained squirrel monkeys on an FR schedule. Completion of the ratio requirement was necessary to ensure occurrence of a time interval in which electric shock was not possible. Regardless of whether or not the animals completed the requirement before or after the first shock, the authors called the behavior avoidance behavior. Azrin et al obviously confounded two behaviors in their explanation. Avoidance was appropriate only if completion of the FR requirement preceded delivery of the first shock; completion of the requirement at some time after shock(s) had occurred was escape from, not avoidance of, scheduled shock.

It is immediately apparent that any schedule of intermittent negative reinforcement will generate avoidance behavior or escape behavior

or some combination of the two. The present study is no exception, hence a second theme of this thesis--that the distinction between the two behaviors is an important one which, rather than being overlooked, must be explicitly made in any experiment involving intermittent negative reinforcement.

III

The above-mentioned themes thus constitute the orientation within which the present experiment was conceived. Over and above this underlying orientation the study had several specific purposes:

(1) the establishment via operant techniques of behaviors characteristic of FR and FI schedules of intermittent negative reinforcement;

(2) demonstration of (a) the avoidance-escape dichotomy with both FR and FI behaviors, and (b) the role of reinforcement in the dichotomy;

(3) examination of the effects of a psychomotor stimulant, methylphenidate, on FR and FI behaviors;

(4) a similar investigation into the effects on FI behavior of reserpine, a psychomotor depressant; and

(5) an examination of the interactive effects on FI behavior of methylphenidate and reserpine, following chronic administration of the latter.

REVIEW OF THE LITERATURE

Since the present study employed squirrel monkeys as subjects, an important paper was that of Kelleher, Gill, Riddle and Cook (1963), which commented on the use of squirrel monkeys in behavioral and psychopharmacological experiments. According to Kelleher et al, squirrel monkeys when handled regularly become tame and tractable, and their small size makes them a convenient experimental subject. The squirrel monkey can be shaped to perform a variety of responses, for example, lever pressing, which can readily be brought under schedule control. The authors found that experimental stresses, such as frequent electric shocks or high drug dosages, render the animals more susceptible to illness, e.g., Appel (1961) reported that the squirrel monkey is sensitive to punishment by electric shock. With respect to its performance in conditioning experiments, Kelleher et al say that the squirrel monkey seems comparable to the Rhesus monkey in its performance on simple or multiple schedules of positive and negative reinforcement.

It is appropriate at this point, with these general notions in mind, to review those studies which, using as subjects not only squirrel monkeys but rats, cats, Rhesus monkeys and pigeons, have employed fixed-ratio and fixed-interval schedules of reinforcement. It should be understood that, whereas there has been a surfeit of experimentation with positively reinforced fixed-ratio and fixed-interval behaviors, there is a paucity of comparable studies involving negative reinforcement. However, it is interesting to note that there is an influential point of view extant which ~~proposes~~ that it is the schedule rather than the nature (positive or negative) of reinforcement which is important in the control of behavior. This view,

proposed by Morse and Kelleher (1966), would render immaterial the disparity in the numbers of studies using the two kinds of reinforcement.

The review breaks down naturally into two sections: (1) behavioral studies, (2) psychopharmacological studies.

I. BEHAVIORAL STUDIES

The defining characteristics of a fixed-ratio schedule of reinforcement were outlined in the Introduction. It is essential to what follows that they be clearly understood.

The post-reinforcement pause is probably the most characteristic aspect of fixed-ratio behavior. According to Ferster and Skinner (1957), as the number of responses in the fixed ratio is increased the pauses following reinforcement grow longer. Felton and Lyon (1966) measured post-reinforcement pausing in four pigeons performing on a range of fixed-ratio schedules from 25 to 150. The results indicated a consistent increase in the length of the pause as the ratio increased. In a similar experiment using rats Winograd (1965) found that when the ratio requirement was increased from FR1 through FR20, the latency of the first response increased with ratio length.

Kaplan (1956) studied both post-reinforcement pausing and response rate in a study of fixed-ratio reinforcement of escape behavior, i.e., termination of an aversive stimulus by a fixed number of skeletal responses occurring in its presence. Under aversive light of 183 m μ L, escape responding of male Wistar albino rats was examined at fixed ratios ranging from 1 to 15 in three animals and 1 to 30 in a fourth. The chief findings were:

(1) Following onset of the aversive stimulus, there tends to be a period of no responding, after which the escape response is emitted at a rapid rate; (2) As the ratio increases, (a) the latency of the first escape response increases exponentially, and (b) rate of escape responding tends to increase. This latter finding is in agreement with a statement by Ferster and Skinner to the effect that "fixed-ratio schedules generate high rates of responding; in the pigeon they often exceed 10 responses per second at large ratios."

The standard reinforcement in fixed-ratio situations involving conditioned aversive stimulation is a period of time-out (T0) from CAS. A number of studies testify to the effectiveness of T0 as a reinforcer. In an experiment by Sidman (1962), monkeys could either postpone shock by pressing a lever or pull a chain to produce a period of T0 from the avoidance procedure; the T0 proved to be an effective positive reinforcer. Verhave (1962) set up a similar situation, in which rats could postpone shock delivery by responding on one lever (avoidance) or produce a T0 by fulfilling a ratio requirement on another lever. On the ratio schedule, rats integrated behavior so well that even at FR 35 they could obtain T0 from the avoidance procedure without receiving a shock. A third experiment was conducted by Azrin, Holz & Hake (1962). Squirrel monkeys were able to earn a 2-minute period during which CAS (a light associated with brief shock on a variable-interval 3 min. schedule) was removed by completing a ratio requirement on a wall-mounted lever. The ratio requirement was increased from 1 to 350 during the course of the experiment. The authors reported a number of findings: (1) T0, i.e., removal

of the stimulus associated with shock, appeared to be the primary source of reinforcement; (2) At ratio requirements less than 50 responses, the subjects began to press the lever almost as soon as the light appeared, maintaining a high rate until the light was turned off. As the ratio requirement was increased, no responding occurred immediately after light onset. The pause was as short as a second at ratio requirements below 50 and as long as 20 minutes at the highest requirement of 350 responses. After each pause, the subjects abruptly began to respond at a high rate, which was maintained until the requirement was completed and the light turned off.

It can thus be taken as proven that T0 from conditioned aversive stimulation is an effective reinforcer of fixed-ratio behavior. But what role does aversive stimulation (e.g., electric shock) play in the maintenance of this behavior? Winograd (1965) held the schedule constant at FR5 while shock intensity was manipulated. Latency of the first response decreased as shock intensity was increased, passing through a maximum for two subjects.

Escape responses of squirrel monkeys were reinforced according to a fixed-ratio schedule by a period of safety from a stimulus that signalled the delivery of intermittent pain-shocks, in an experiment by Azrin, Holz, Hake, & Allyon (1963). The frequency of shock was gradually reduced, but the performance remained at a high level until the shocks were quite infrequent. Aversive stimulation thus effectively maintained FR behavior.

From the studies cited above it would appear that fixed-ratio behavior is in general quite stable. This is the case, however, only if the schedule does not impose too strenuous a requirement on the animal.

For example, Thompson (1964) allowed rats to terminate the FR stimulus control by pressing a T0 lever throughout both ascending and descending FR sequences, three responses being required to produce a 30 sec. safe period (S^{Δ}). As FR performance became more "strained" there was an increased predisposition to escape from the time-in stimulus complex. This finding will be of importance to the interpretation of the erratic performance of one of the subjects in the present study on a high-valued fixed ratio--FR 250.

To recapitulate, the studies cited above have demonstrated a number of empirical facts about fixed-ratio behavior:

1. Fixed-ratio schedules generate high rates of responding;
2. The higher the FR requirement, the longer the post-reinforcement pause and the higher the response rate following the pause;
3. ^{T0 from} Δ conditioned aversive stimulation is an effective reinforcer of fixed-ratio behavior;
4. Electric shock, even if it is infrequent, is effective in maintaining fixed-ratio behavior, with the latency of the first response varying inversely with shock intensity; and
5. Fixed-ratio behavior is stable, although ratio-strain may be induced by too high a ratio requirement.

The other schedule employed in the present study was FI 180 sec., with a limited hold 2 sec. contingency operative, i.e., unless a response was made in the 2 sec. following termination of the interval, a shock was delivered, and every 2 sec. thereafter, until a response was made. A number of studies in the literature are germane to such a fixed-interval schedule.

According to Ferster and Skinner (1957), "a fixed-interval schedule normally generates a stable state in which a pause follows after each reinforcement, after which the rate accelerates to a terminal (usually moderate) value." The positive acceleration in response rate, as evidenced on the cumulative record, is known as a scallop. One explanation for the development of a scallop is this: the longer the interval since the last response, the more likely the next response is to be reinforced, hence the latency between responses grows less as reinforcement becomes imminent.

But what is the effect of the addition of a T0 contingency? "At shorter fixed intervals (up to 4 min.) introduction of a T0 after reinforcement increases the overall rate by eliminating the post-reinforcement pause and curvature" (Ferster and Skinner, 1957). This effect of T0 can be largely offset by the introduction of a limited hold (LH) contingency at the end of the fixed interval. Hearst (1958) successively decreased the LH from 30 sec. in an experiment with four pigeons, for which the response was key pecking and the schedule a "time-correlated contingency" (Schoenfeld, Cumming and Hearst, 1956). The result of reduction of the LH was a behavior pattern consisting of a pause after the end of the T0, followed by an accelerating high rate of responding. In summary, it would appear that the LH contingency offsets the tendency of T0 after reinforcement of short fixed intervals to reduce the pause and scallop characteristic of fixed-interval behavior.

Though T0 attenuates the characteristics of fixed-interval behavior, it is an effective reinforcer of that behavior. In the experiment by Verhave (1962), rats could postpone shock delivery by responding on one lever (avoidance), or produce a T0 by fulfilling an interval requirement on another

lever. Even at FI 15 min., the animals only occasionally spent unnecessary time on the avoidance lever.

Shock intensity has an important influence on fixed-interval behavior. With rats in a lever-pressing situation on a variable-interval schedule, Dinsmoor and Winograd (1958) found that when the intensity of shock was raised or lowered the transition to a new response rate was usually immediate. The rates were roughly proportional to the level of current, i.e., it would appear that response rate has a direct functional relationship to shock intensity. Though the study used a variable-interval schedule, it is reasonable to assume that a similar relationship holds for fixed-interval schedules.

Dinsmoor (1962) demonstrated the effectiveness of electric shock in maintenance of lever pressing behavior on an interval schedule. Widely and irregularly spaced pulses of shock were accompanied by originally neutral visual and auditory stimuli; a bar press ended the shocks according to a variable-interval schedule. A control procedure was identical except that there were no visual and auditory stimuli present. The findings were as follows: (1) Bar pressing under the control procedure was attributable to differences in the relative aversiveness of pressing and non-pressing due to differences in the incidence of shocks following the two kinds of behavior. (2) Rate of responding increased with the visual and auditory stimuli over the rate engendered by the control procedure; this was attributed to termination of conditioned aversive stimulation associated with the occurrence of electric shock.

Experiments employing differential reinforcement of specific inter-response times have yielded schedule control of response rates. For example, a study by Kelleher, Fry and Cook (1959) studied the acquisition of fixed-interval behavior in rats on two schedules: the first reinforced responses spaced 18-21 seconds apart; the other reinforced all responses occurring more than 20 seconds after a previous response. With prolonged exposure to either schedule, the response probability became dependent upon time since the previous response. In other words the pattern of responding engendered by the schedule was determined by the terminal inter-response time (the inter-response time concluded by reinforcement).

This popular point of view was challenged by Dews in two studies in which he trained pigeons (1962) and squirrel monkeys (1965) on an FI 500 TO 250 schedule. The fixed-interval was divided into ten 50 sec. periods. During periods 2, 4, 6, 8 and 10 a bright white light was repeatedly presented. In the presence of the white light a response was never immediately reinforced; the white light thus functioned as S^Δ . Responding was interrupted during the S^Δ periods but in both the squirrel monkey and the pigeon these interruptions did not destroy the characteristic scalloped pattern of the cumulatively recorded responding through each interval.

In explanation, Dews said ". . . there appears to be an underlying gradient of increasing tendency to respond that continues through the interval," and further, ". . . the progressive increase in rate of responding through the fixed interval would be based on a declining retroactive rate-enhancing effect of the reinforcing stimuli as the delay between response and reinforcement is increased."

It is important to note at this point that Dews extends his interpretation to fixed-ratio behavior, the modus operandi of which he says is also erroneously based on the assumption of the pre-eminent importance of the final inter-response time.

. . . the high rates of responding engendered by fixed-ratio schedules may come about as follows: The higher the average rate of responding on an FR schedule, the closer temporally, the initial response and all subsequent responses in the FR are to reinforcement, and, therefore, the greater the retroactive enhancing effect of that reinforcement. This will tend to increase the rate of responding, which in turn will bring the response closer to reinforcement, which will increase the rate further.

Whichever explanation of fixed-interval behavior is correct, Dews' experiments would appear to demonstrate the relative stability of fixed-interval behavior in the presence of added stimuli. However, Ferster and Zimmerman (1963) were not able to generate such stability. They examined the performance of two monkeys on fixed-interval schedules with added visual, auditory or combined auditory-visual clock. (A clock is a stimulus some dimension of which varies systematically with time, e.g., as reinforcement comes closer temporally, the illumination from a wall-mounted light increases.) Despite the presence of a LH contingency, the response rates of the monkeys were often extremely low.

In summary, the literature on fixed-interval behavior cited above permits a number of conclusions:

1. Fixed-interval schedules generate stable behavior, characterized by a pause after reinforcement followed by an accelerating moderately-valued response rate;

2. At low FIs, the addition of a T0 after reinforcement tends to increase the overall response rate by reducing curvature and the pause after reinforcement; this tendency can be largely eliminated by the utilization of a short duration LH contingency;

3. T0 is an effective reinforcer of fixed-interval behavior;

4. Response rate on a fixed-interval schedule varies directly with shock intensity; and

5. Conflicting evidence exists as to the effects of added stimuli on the stability of fixed-interval behavior, and there are two well-supported, but widely divergent, interpretations of what determines the pattern of responding engendered by fixed-interval (and fixed-ratio) schedules of reinforcement.

Having dealt with the literature on fixed-ratio and fixed-interval schedules separately, it is appropriate at this point to review the literature dealing with the two schedules in combination. One method of combination programs reinforcement by alternating the two schedules, each schedule being accompanied by an appropriate stimulus so long as the schedule is operative. This is a multiple schedule of reinforcement.

An extensive series of experiments, employing squirrel monkeys responding from a restraining device on a multiple FR-FI schedule, was reported by Morse and Kelleher (1966). The experiments were based on the following fact: that "the termination of a schedule complex, comprising a stimulus in the presence of which brief presentations of electric shock are scheduled, is a reinforcer." In all experiments, in the presence of a red stimulus, subjects had to complete a ratio requirement on a wall-mounted lever to obtain T0 from regularly occurring electric shock. In

the presence of a white stimulus, in order to earn a T0 subjects were required to make a response during time "t", the time between the end of the fixed interval and the first scheduled shock; in effect, "t" was a LH contingency.

In Experiment I, the terminal schedule was a multiple FR 30 FI 10 min. (t 1 sec.) schedule. Two monkeys were maintained on this schedule for 10 months. "Over this entire period, characteristic fixed-ratio and fixed-interval patterns of responding were obtained."

Experiment II investigated the effects on the subjects from Experiment I of omission of scheduled shock in a multiple FR 30 FI 10 min. (t 1 sec.) schedule. ". . . when shocks were omitted, responding in many FI 10 min. components decreased to near zero, while relatively high rates of responding were maintained in FR 30 components."

The authors concluded from Experiments I and II ". . . that multiple schedules of schedule-complex termination can engender steady state patterns of responding comparable to those obtained with multiple schedules of food presentation."

Experiment IV examined the effects on responding on an FI 5 min. schedule, of decreasing the length of "t" from 15 sec. to 1 sec. "Decreasing the value of t generally increased average rates of responding and produced positively accelerated responding within fixed-interval components." The conclusion confirmed the major finding of Experiment I that it is on the parameter value of the shock schedule in the fixed-interval schedule complex that the development of a positively accelerated pattern of fixed-interval responding depends.

In Experiment V, responding in the fixed-interval component of an FR 30 FI 10 min. multiple schedule in which t was 0 sec. was well maintained for more than six months.

This series of experiments documents extremely well the range of parameters over which it is possible to generate characteristic fixed-ratio and fixed-interval patterns of responding. That these behaviors were maintained for many months is proof of the stability of the behavior patterns generated.

However, the most interesting pronouncement arising from this pedestrian series of experiments is the authors' suggestion ". . . that the schedule of reinforcement is more important in the control of behavior than is the nature of the reinforcer," the basis of which is their observation that "fixed-ratio and fixed-interval terminations of schedule complexes [using noxious stimuli] can engender the characteristic patterns of responding usually obtained using these schedules with food presentation."

II. PHARMACOLOGICAL STUDIES

Behavioral base lines with several reproducible properties are useful in investigating the effects of drugs on learned behavior. Differential drug effects on interrelated characteristics of behavior make possible detailed analyses of drug action. In addition, behavioral base lines with complex properties offer an advantage in that they are more sensitive to the effects of drugs than are simple base lines.

(Morse and Herrnstein, 1956)

There are a number of alternative ways in which drug literature can be surveyed: (1) pharmacological analyses of biochemical-behavioral

interrelations; (2) drug-behavior interactions; and (3) the effects of specific drugs, and specific classes of drugs, on behavior. The last alternative is best suited to the purposes of the present study. Consequently the review presented here will comprise three sections:

(a) studies concerned with the effects of stimulant drugs, specifically methylphenidate, on behavior;

(b) studies concerned with the effects on behavior of the Rauwolfia-derived depressant drug, reserpine; and

(c) studies concerned with the interactive effects on behavior of stimulant and depressant drugs, specifically methylphenidate and reserpine.

(A)

While the exact nature of the behavioral effect may differ, certain drugs share the ability to increase response rate while other drugs share the ability to decrease rate. Following common pharmacological practice, the rate-increasing drugs can be called stimulants, and the rate-decreasing drugs can be called depressants. Notwithstanding the fact that such terms may oversimplify drug effects (e.g. a drug may increase response rates at low doses and decrease rates at high doses), Boren (1966) derived a six-part classification of representative behavioral drugs--stimulants, antidepressants, depressants, anticholinergics, hallucinogens and analgesics. The studies reviewed below employed methylphenidate or the related stimulants, amphetamine, methamphetamine or caffeine.

A typical experiment was performed by Weiss and Laties (1964). Characteristic control baselines were generated in pigeons performing on an FI 5 min. schedule, in which the reward consisted of 3 sec. access

to grain. Injection of amphetamine-sulfate at a dosage of 2 mg./kg. lead to an increase in the number of responses made per interval, a result attributable largely to the animal responding steadily at the beginning of the interval, a time when, under normal conditions, there is little or no responding. Similar results were reported by Dews (1958).

A host of studies have shown this rate-increasing effect of amphetamine in situations involving aversive control techniques. For example, Hearst and Whalen (1963) demonstrated that, in a discriminated avoidance situation, d-Amphetamine (3 mg./kg.) increased the number of responses made and hence, shocks avoided. Teitelbaum and Derks (1958) showed that, under certain doses of amphetamine, shock avoidance responding (electronically-monitored water drinking) increased and was sustained, even when the experiment and its associated stimuli were terminated. Amphetamine increased the output behavior of rats trained to terminate a very loud noise by pressing a lever (Harrison & Abelson, 1959).

Pecking was food-reinforced on a fixed-ratio 300 schedule in a study by Ferster, Appel & Hiss (1962). Responses made during a red light produced a TO. If the pigeon did not respond during the red light, the light terminated, and the FR could be completed without interruption. The birds were soon avoiding most of the possible TOs. The pre-TO stimulus produced FR strain and extreme curvature atypical of normal fixed ratios of this magnitude.

. . . d-amphetamine injected when the FR performance was strained by the pre-time-out procedure produced marked increases in responding. The drug administration lowered

the rate of responding only at larger doses, and then this occurred predominantly just after injection.

It would appear that the response rate-increasing effect of the amphetamines is well established. The most sophisticated interpretation of this phenomenon has been offered by Dews, on the basis of a series of studies in the late 1950s.

Whereas amphetamine in general produced an increase in responding in rats (Skinner & Heron, 1937; Sidman, 1956; Brady, 1956), Dews (1955b) found little increase in the output of pecking behavior of pigeons with methamphetamine in a free operant situation. Rather than attributing the absence of a substantial stimulant effect to a species difference between rats and pigeons, or to a difference between amphetamine and methamphetamine, Dews (1958) suggested the difference might be due to the nature of the performance engendered by the schedule of reward used. He therefore tested pigeons on the following schedules: VI 1 min., FR 50, FI 15 min. and FR 900, obtaining this result:

The most obvious difference between the performances on FI 15 min. and FR 900 and the performances on VI 1 min. and FR 50 is that the former pair of schedules gives rise to sustained pecking at a fairly constant rate while the latter pair characteristically gives rise to varying rates and periods with no pecks. This difference seems to be responsible for the differential effect of methamphetamine. The results can probably best be stated in terms of inter-response times, i.e., the time elapsing between consecutive responses. It is suggested that, in appropriate doses, methamphetamine tends to reduce the number and length of inter-response times in excess of 5 seconds but that rather large doses also tend to prolong inter-response times shorter than 1 second.

Dews proposal was thus twofold: (1) Psychomotor stimulant drugs (e.g., the amphetamines) increase rates of operant responding under schedules that engender low rates and decrease the output of

responses under schedules producing higher rates; and (2) the effects of such drugs are determined largely by the frequency of occurrence of the response being studied.

It is sufficient at this point to cite only two of the numerous experiments that have verified Dews' proposal. Kelleher & Morse (1966) examined in individual squirrel monkeys the effects of d-Amphetamine on fixed-interval responding maintained by the presentation of food and the termination of a stimulus-shock complex. Performances characteristic of FI 5 min. developed in each animal. Average response rates increased following 0.1 and 0.3 mg./kg., i.m., of d-Amphetamine, but decreased following larger doses. As in previous studies, the magnitude of the rate-enhancing effects of d-Amphetamine depended upon control rates of responding.

With pigeons trained to respond on a multiple FI 300 sec. FR 33 schedule, Smith (1964) found that d-Amphetamine increased rates of responding during portions of the schedule characterized by low rates of responding, and suppressed response rate during the schedule component characterized by high rates.

While most of the work on psychomotor stimulants has been done with the amphetamines, some studies have been concerned with the effects of caffeine and, since its appearance in 1954, methylphenidate. Methylphenidate being one of two drugs employed in the present study, a detailed examination of the relevant literature is appropriate at this point.

The first study employing methylphenidate was a pharmacological analysis of the drug by Meier, Gross & Tripod (1954). The psychomotoricity

due to methylphenidate in a number of experimental animals (mice, rats, rabbits, dogs) upon parenteral or oral administration was characterized as follows:

Aside from general restlessness, the experimental animals show a coordinated increase in mobility, especially in the form of an urge to move about and run and an urge to eat or gnaw, without becoming snappish and aggressive. Depending on the animal and species and mode of administration, this central stimulating effect appears after doses of 0.5-1.5 mg./kg., lasts for several hours and then subsides, leaving signs of fatigue. Larger doses of methylphenidate produce an ataxic gait and clonic-tonic convulsions.

This effect, the authors point out, is generated by a drug which has a relatively low toxicity. They conclude that as to its type of effect, methylphenidate must be classified, on the analeptic continuum, somewhere between amphetamine and caffeine.

Using rats that had been trained on both a fixed-interval and a fixed-ratio schedule, Mechner & Latranyi (1963) were able to accurately distinguish three closely related psychomotor stimulants on this continuum --methamphetamine, methylphenidate and caffeine.

Fixed-interval and fixed-ratio, two of the behavioral procedures employed, proved to be the best discriminators of the difference between the behavioral effects of the three drugs. Both schedules involved a 2-lever situation. When the fixed-interval schedule was in effect, the rat was required to make a response on bar A to initiate a 30 second interval, following expiration of which the first response on bar B was reinforced by 0.03 c.c. of water from a liquid dispenser. The animals exhibited typical fixed-interval behavior, pausing after initiating the interval and then responding at a gradually accelerating

rate on bar B 'til reinforced. The results showed immediately that all three drugs produced an increase in the number of responses on bar B. Caffeine, however, was found to be much less effective than either methamphetamine or methylphenidate in this respect, to a statistically significant degree. Also, caffeine did not destroy the temporal discriminations of the subjects, as did the other two drugs, at higher dosages (12 mg./kg. and 24 mg./kg.).

The fixed-ratio schedule demanded 46 responses on bar A before a response on bar B was reinforced. The subject typically paused following a reinforcement, completed a large proportion of the FR requirement before making the first bar B response, then alternated between the bars, with an increasing number of responses on bar B, until the ratio requirement was completed. Under fixed-ratio, the three drugs again generated increased responding on bar B, but in this case the effect was comparable with methylphenidate and caffeine and much less marked with methamphetamine.

The authors conclusions were three:

- (1) Doses of caffeine that produced a manifold increase in the frequency of responses on bar B per reinforcement under fixed-ratio produced a negligible increase in the same measure under fixed-interval.
- (2) On the other hand, doses of methamphetamine that produced maximal increases under fixed-interval had a very small effect under fixed-ratio.
- (3) At the peak of its dose-effect curve, methylphenidate had the behavioral effects of methamphetamine under fixed-interval and the behavioral effects of caffeine under fixed-ratio.

This differential effect of methylphenidate on fixed-interval versus fixed-ratio behavior is of importance to the present study, which employed the same two schedules.

Some further effects of methylphenidate on schedule-controlled behavior were reported in a study by Stretch, Blackman and Alexander (1966). A rat was trained on an avoidance schedule, which included a warning signal, on which a single response on a wall-mounted lever reset the response-shock interval, thus postponing shock. The animal was then placed on a multiple schedule, in which the first component was the same as before, while the second component required four lever presses to delay shock. The behavior generated by the FR 4 requirement resembled that of the behavior on the single-response component, since responding was controlled by the warning signal in both cases; however, more shocks were received in the FR 4 component. Two mg./kg. methylphenidate, injected intraperitoneally immediately pre-session, reduced shock frequency during FR 4 components, while leaving FR 1 behavior unaffected; 4 mg./kg. impaired stimulus control during both components. Response distributions of two further animals working exclusively on an FR 4 avoidance schedule showed that methylphenidate increased response rates prior to the onset of the warning signal, i.e., stimulus control of ratio avoidance behavior was impaired (although shock frequency was reduced due to the overall increase in response rates).

Two studies of a more general nature, dealing with alterations in behavior by methylphenidate at high dosage levels, must be considered before attention is focussed on psychomotor depressant drugs. The behavioral effects of large dosages of methylphenidate on a conditioned response were reported in a study by Faidherbe, Richelle and Schlag (1952). Liquid-deprived cats were put on a schedule in which an auditory stimulus (S^D = weak buzzer) signalled the end of a 75 sec. interval (S^Δ) and remained on

until the response (introducing the forepaw into a cubic hole in the wall of the cage) was given. Responses in S^{Δ} were ineffective; the reinforcement (2 ml. milk) was delivered, and S^D terminated, after one response in S^D . In both cats, 2 mg./kg. methylphenidate, administered subcutaneously immediately pre-session, had only a slight effect on the highly stable behavior generated by the schedule, interfering very little with the regular responding at the onset of S^D . With the first injection of the large dose of 6 mg./kg., cat 6 ignored 24 of the 50 reinforcements earned in the first session, and showed a marked increase in the number of responses in S^{Δ} . Cat 4 responded as regularly as before at the onset of S^D but ignored 50 of 85 reinforcements. In subsequent experiments, during all drug sessions this cat showed a generalized agitation which completely excluded the conditioned response.

Of most importance to the present study is the authors' description of the whole activity of the subject continuously observed in the experimental cage.

The drug generates a state of generalized excitation, in which a bit of behavior--whether it is a highly automatized conditioned response or anything else from the animal's natural repertoire, such as licking its paw or moving its head forward rhythmically--tends to recur and repeat itself for a long time.

Drug-induced perseveration of inappropriate behavior would thus account for the animals ignoring the reinforcement.

While the above study used cats, an experiment by Davis (1957) explored the gross effects on overt behavior of moderate doses of methylphenidate in normal Rhesus monkeys. The drug produced an increase in spontaneous motor activity of monkeys in a photo-cell device. The

general impression was one of extreme alertness on the part of the animal. Minor sounds from outside the test area produced long-lasting visual and auditory attention. Visual interest in the long familiar test environment was intense. This effect was only produced, however, over a narrow dosage range. In no case was any visible effect produced by quantities less than 0.5 mg./kg.; 1 mg./kg. produced a slight increase but 2.5 mg./kg. produced a large decrease. Interestingly, the decrease in motor activity at the high dosage level was selective, that is, "leaping" between two pairs of bars was practically unaffected but "pacing" fell to as little as 5% of control levels.

The drug did not seem to have any cumulative effect, but rather, a certain amount of tolerance developed to repeated doses of the drug, at least when activity reduction was the criterion of effectiveness used.

From the studies cited above, it can be said of methylphenidate that it is a psychomotor stimulant which (1) causes a coordinated increase in on-going behavior at dosages up to 2-4 mg./kg. but uncoordinated ataxic disruption in functioning at higher dosage levels, and (2) has characteristic but differential effects on behaviors generated by different schedules of reinforcement, specifically fixed-ratio and fixed-interval.

(B)

According to the classification by Boren (1966), depressant drugs are subdivided into two groups, barbiturate hypnotics and tranquilizers. With respect to the latter, Boren distinguishes three classes--Rauwolfia alkaloids, phenothiazine derivatives, and muscle relaxants. The Rauwolfia alkaloids (compounds derived from the Rauwolfia

root, which has been used medicinally for centuries in India), consists of rescinnamine, deserpidine and reserpine. The depressant used in the present study was reserpine, a drug the behavioral effects of which are well documented in the literature.

Observations were made on the rope-climbing performance of eight male albino rats during reserpine treatment. Acheson, Cole, Dearnaley and Dearnaley (1961) administered 5 mg./kg. of reserpine subcutaneously, daily for 8 days, with two main results: Reserpine (1) disrupted climbing, and (2) produced a characteristic symptom-complex (syndrome) in all subjects--a strongly down curling tail, a strong grasp reflex, closed eyes, piloerection, tremors, diarrhoea, hunched posture and greatly decreased activity. In the same vein it is interesting to note that Davis (1957), Weiskrantz (1958) and Trouton and Eysenck (1961), observed that reserpine, particularly very heavy doses, produced Parkinson-like symptoms in experimental animals.

Numerous studies have explored the effects of reserpine on a conditioned emotional response (CER), with widely divergent results. Briefly, the CER technique involves the inhibition of a stable response by the effects of a previously neutral stimulus that has been paired with a noxious condition. The inhibition of a response in this manner is presumably a function of anxiety associated with pain, and provides a base from which drug effects can be assayed.

Yamahiro, Bell and Hill (1961) conditioned 20 male Wistar albino rats to inhibit a lever pressing response during a four min. tone period which was terminated by a strong electric shock (CER). Two groups of ten animals, matched on the basis of response rate during pre-tone and tone

periods, were tested concurrently for 18 consecutive days, with the experimental group receiving a daily and periodically increasing subcutaneous dose of reserpine (0.2-0.6 mg./kg.). It was found that reserpine produced no significant effects on the CER when compared with that of the matched control group. Brady (1956b), using Rhesus monkeys, found that 0.75 mg./kg. of reserpine daily increased lever pressing during a "clicker-on" period and decreased it during "clicker-off".

The results obtained by Yamahiro et al and Brady may be contrasted with the findings of Valenstein (1959), on the effects of reserpine on conditioned emotional responding in the guinea pig. A CER procedure (three min. presentation of clicker, terminated by a 2 sec. 2 mA. shock) was superimposed on established water-reinforced variable-interval lever-pressing behavior. With a reserpine dosage level of 0.003 mg./kg., there occurred a 50% decrease in lever-pressing rate during the non-clicker period and a marked diminution of responding during the clicker period; responding was suppressed almost completely, except for brief bursts during the clicker period, when the dosage level was increased to 0.03 mg./kg.

Obviously, the effects of reserpine on conditioned emotional responding are as yet not clearly understood, with the tendency of the guinea pig to respond reduced by doses of reserpine on the order of 100 times less than those required in the rat or monkey. Dews and Morse (1961) summarized the situation: "The difference between the results in rats and monkeys and in guinea pigs is attributed to a species difference, but it is clear that these fascinating but complex phenomena deserve further analysis."

Another area in which reserpine holds definite, but again equivocal, consequences for conditioned behavior is that of reinforcement. Wenzel (1959) trained eight cats to press one lever in the presence of one stimulus to obtain food and a second lever in the presence of another stimulus to avoid or escape electric shock. The latency of response was increased much less to the food lever than to the shock lever, hence Wenzel's conclusion that the type of reinforcement played a crucial role in determining susceptibility of the responses to the effects of reserpine.

Equivocal or even contrary findings were reviewed by Sidman (1959), who concluded that the classification that seemed to be developing for reserpine on the basis of positive versus negative reinforcement contingencies did not hold.

Ambiguous as the results of the above studies are, reserpine does appear to have a depressant effect, one facet of which is, in almost all instances, a decrease in conditioned responding. This effect is apparent in studies of escape and avoidance conditioning, and here the results are more or less unequivocal. For example, complete loss of both avoidance and escape responding occurred in a cat eight hours after administration of 0.07 mg./kg. reserpine (John and Killam, 1959); reserpine at 0.37 mg./kg. caused a 50% loss of avoidance responding in a monkey (Smith, Wagman & Riopelle, 1956).

Leg flexion was the avoidance response in a study by Domino, Karoly and Walker (1963). Responses in the presence of a tone postponed shock (avoidance), while a response within five seconds after shock onset terminated shock (escape). If a response did not occur within 5 seconds,

the intensity of shock gradually increased from an initial level of 0.7 mA to 7 mA. Avoidance responses failed to occur at a dosage of 0.1 mg./kg. reserpine, and escape responses also stopped, though not at the higher shock levels.

In the light of these escape-avoidance studies, and the others reviewed above, a valid generalization may be made: that in studies involving the conditioning of a particular motor response, a relatively small amount of reserpine produces a marked reduction in the frequency of occurrence of that response.

What is the cause of this phenomenon? Davis (1957) provided an answer in a study using Rhesus monkeys. In a test chamber equipped with photo-cells the animal had the choice of either pacing the floor or leaping between two pair of bars. Reserpine was injected daily (i.m.), 2 hours before the start of activity testing. In all subjects, locomotor activity was reduced by very small doses of reserpine, for example, locomotion of monkey A was totally arrested by a dose of only 0.18 mg./kg. daily. The minimally effective dosage reduced spontaneous activity by a third to a half, while the subjects remained normally aggressive, and normally responsive to various external stimuli. As the dosage was increased, spontaneous locomotion gradually disappeared completely, though animals still moved freely in response to appropriate stimuli. Spontaneous activity of any kind was completely eliminated by the use of large doses, with the animals showing apathy, stereotyped postures held for long periods, but rarely sleep. A cumulative effect of successive doses of reserpine was recognized, with the maximum effect of a designated dosage being achieved within three to seven days.

One animal, after 8 days on 0.3 mg./kg. daily, developed a Parkinson-like tremor which disappeared after 36 hours without further drug, and did not reappear during another reserpine series of equal length but smaller dosage which was carried out two weeks after the tremor episode.

That the reduction in conditioned responding produced by reserpine is a by-product of an overall decrement in locomotor activity is a superficial explanation. The basic question is, what is the mechanism involved in the reduction of locomotor activity? One answer was suggested by Riopelle and Pfeiffer (1958). Two experiments were performed. In the first, three Rhesus monkeys received injections of 0.5 mg./kg. of reserpine daily for 18 days. During this period they were tested on multiple-discrimination, conditioned avoidance and delayed-response tasks. All subjects showed many response failures in the fourth hour after injection, but recovery was nearly complete by the eighth hour.

In the second experiment, four monkeys received daily injections of 0.25 mg./kg. of reserpine for 66 days. After a five-day rest, they received 0.5 mg./kg. of reserpine for 14 days. Two important findings were obtained. Firstly, the animals showed reduced susceptibility to the drug, as measured by conditioned avoidance and general behavior; in other words, a certain amount of tolerance developed to reserpine. Secondly, a great response decrement was shown on the two tasks involving reward. The authors suggest that, with respect to the decrement in the number of responses attempted on all tasks, "the alterations which follow injection of reserpine are not restricted to behavior associated with fear, anxiety, or avoidance of noxious stimuli. Instead, decrement in

approach behavior associated with rewarded stimuli also occurs. It would seem, therefore, that reserpine causes a more general reduction in motivation, at least in that motivation arousing the organism to muscular action."

As operant pharmacology developed, a number of alternative explanations for the effects of reserpine were forthcoming.

A biochemical explanation, based on reserpine-induced release and subsequent breakdown of monoamines, was proposed by Heise and Boff (1959). [Perhaps equally important was their finding that 2 mg./kg. tetrabenazine, a benzoquinazoline derivative that like reserpine has marked sedative and tranquilizing activity, when administered subcutaneously immediately pre-session to rats working on a Sidman avoidance schedule, caused responding to cease completely in about 20 minutes, a suppression which lasted approximately 3-8 hours. In other words, the behavioral effects of tetrabenazine were very similar to those of reserpine.]

Weiskrantz (1958) formulated a hypothesis which assumed that behavioral non-reactivity under reserpine occurred because the organism no longer received any sensory information--that the input was cut off. Stated in its most extreme form, the hypothesis was that "the animal is just like one who is deaf, blind, and deprived of all other sensory information, including feedback from its own behavior and internal stimulation."

To prove that the non-reactivity was not simply a loss of behavioral output, Weiskrantz carried out a study involving a conditioned fear situation in which a neutral white noise signal was presented 30 seconds before a strong and unavoidable electric shock. Control animals

responded by running, crawling, and showing signs of intense disturbance. Reserpinized monkeys showed no change in behavior when the noise came on, and responded to shock only on a tetanic basis. The interesting question was whether, once the drug had worn off, the animals would show evidence of having learned anything in the situation. The answer was negative, that is, the reserpine monkeys required, on the average, about as much training to reach criterion as the control group had required in the first place. "Functionally then, it was more or less as if the reserpine animals had never been in the situation; it was like dead time for them." In summary, Weiskrantz' suggestion was that behavioral non-reactivity in reserpinized animals was a function of the fact that reserpine stimulates the very neural centres which produce sensory blockade.

Still a third explanation for the behavioral effects of reserpine developed out of a study by John, Wenzel and Tschirgi (1958). Eight cats were trained to 100% accuracy to avoid shock in a hurdle box within 5 seconds of presentation of either an auditory (1200 cy/sec. tone) or a visual (darkened compartment) stimulus. Under reserpine, administered intramuscularly over a range of 7.5 μ g. to 65 μ g./kg., performance was adequate only to the auditory stimulus, the visual stimulus presentation being followed only by arousal. The data suggested to John et al that reserpine had not blocked the anxiety-evoking potential of the conditioned stimuli, nor blocked the conditioned avoidance response by interference with sensory perception, with motivation to perform, or with motor coordination. Therefore, they proposed that this "selective action of reserpine may be attributed to an interference with the specific conditioned association between the stimulus and a directed evasion response--that is, interference with learned associations."

The above rather labored treatment of the effects of reserpine is necessary background to the fact that during the last decade dissatisfaction with these biochemical, motivational, emotional and learning versus performance explanations of the effects of drugs on behavior has become increasingly pronounced. The fundamental difficulty with all these explanations is that differential effects of a drug can often be seen on behaviors which have the same motivation, comprise the same response, or occur in the same animal during successive short periods of time; and which differ only as a result of certain procedural differences. The fact, therefore, that reports of reserpine effects, for example, have not always been uniformly replicated has led to a growing appreciation of the importance of environmental contingencies--such things as reinforcement schedule, duration and frequency of presentation of stimuli, and shock intensity--in determining drug effects on behavior. These environmental contingencies, in summary, relate to the programming of the temporal and sequential relations between stimuli presented to an animal, responses of the animal, and further stimuli consequent upon those responses. The first and last of this series of events together comprise a "schedule." These are not trivial matters, but rather,

. . . the importance attributed to schedules in determining behavior has been growing steadily since the days of Pavlov, and they are now beginning to overshadow the traditional variables--motivations, emotions, etc.--that, ever since the Greeks formulated them, have been supposed to be the essential and only determinants of behavior.

(Dews and Morse, 1961)

Awareness of this fact has resulted in recent years in repeated demonstrations that the behavioral effects of a drug are frequently critically dependent on schedule influences on behavior.

One drug for which this interpretation has been found to hold is reserpine. The observation that reserpine blocks avoidance responses at dosage levels lower than those at which escape responses are impaired has been reported above. In explanation, in place of the traditional analogy to the clinical situation (i.e., fear is lessened but pain-motivated responses are unimpaired) Dews and Morse have proposed that

. . . reserpine may weaken "stimulus control" of behavior, rather than produce specific effects on "fear". That is to say, the control of behavior by exteroceptive and interoceptive environmental stimuli may be disrupted with the result that reserpine interferes with positively reinforced (rewarded) behavior as well as aversively controlled behavior.

(Gollub & Brady, 1965)

This interpretation was based on a study by Dews (1956) with pigeons trained on a food-reinforced multiple FR 60 FI 15 min. schedule. Under the influence of 100 μ g./kg. reserpine injected intramuscularly, ratio behavior was characterized by pauses not found in the non-drug state. The author's conclusion was that reserpine liberated the pigeons from the normally powerful stimulus control of the schedule.

To conclude this penultimate section of the literature review, it may be said that (1) reserpine has a suppressant effect on conditioned behavior, producing marked diminution of responding at very low dosage levels, and complete cessation of behavior at high dosages, and (2) the most plausible explanation of the suppressant action of reserpine is that the drug disrupts the stimulus control of the schedule over behavior, a fact which calls attention to the central role of the drug-behavior interaction problem in behavioral pharmacology.

(C)

The remaining area to be reviewed is that dealing with the combination effects of psychomotor stimulants, most importantly methylphenidate, and a specific psychomotor depressant, reserpine.

That the reserpine-induced suppression of behavior can be counteracted by psychomotor stimulants has been documented in a number of studies. Two will be reviewed here. In the first, Seiden & Hanson (1964), working on the knowledge that 3,4-dihydroxyphenylalanine (DOPA) can temporarily counteract in rats the reserpine-induced suppression of motor activity and conditioned avoidance responding (CAR), designed a study to investigate the effects of L-DOPA on the reserpine-induced suppression of CAR in the cat. Reserpine at 0.1 mg./kg. produced slight ptosis and marked miosis, a decrease in CAR (movement from one compartment to another in a shuttle-box) from 90% to 25%, and abolition of escape responding by the end of the session. Intraperitoneal injection of 100 mg./kg. of L-DOPA, dissolved in 0.9% sodium chloride solution, produced a return to the pre-reserpine performance in four cats and a partial recovery in five more. The effect lasted no more than half an hour, and was followed by deterioration to levels below the pre-DOPA-reserpine level.

The actual "antagonistic" effects of reserpine with a psychomotor stimulant, amphetamine, were studied by Rech (1964). One hundred and ten female rats were trained to 50% successful avoidance in a shuttle box in which a 600 cy./sec. tone was the conditioned stimulus which preceded shock by 5 seconds. A dosage of 2 mg./kg. of reserpine was injected intraperitoneally, and the subjects were tested 2.5, 8, 24 and 48 hours later. Immediately following each of these sessions, a

2 mg./kg. intraperitoneal administration of d-Amphetamine was made, with the subjects being tested 30 minutes afterward. The repeated d-Amphetamine dosages were not expected to have any cumulative effect, since the drug is fairly rapidly metabolized and no trace of it is found in the brain four hours after intraperitoneal injection. The behavioral effects of reserpine were completely abolished by the d-Amphetamine and performance was enhanced up to 8 hours after reserpine administration. Due, however, to hyperactivity induced by the stimulant when it was injected at the 24 and 48 hour stages, performance again deteriorated due to the less potent effects of reserpine at these stages.

The first description of the interaction between methylphenidate and reserpine is found in the study by Meier, Gross and Tripod (1954). The authors found that reserpine, acting mainly on substrates in the brain stem, inhibited the psychomotor effect of methylphenidate, the dose of reserpine needed to inhibit methylphenidate's motility-increasing action on mice being less than that needed to inhibit the amphetamine effect.

Cole and Glees (1957) made a detailed examination of the gross behavioral changes produced in Rhesus monkeys by reserpine plus methylphenidate. Reserpine alone, given intramuscularly in large doses (5 mg., 2.5 mg. and 1 mg./kg.) produced the characteristic syndrome, with subjects adopting a "foetal" position and finally, a catatonic-like state. When a monkey fully under 5 mg./kg. of reserpine was given 20 mg./kg. of methylphenidate (subcutaneously), a striking and sudden change occurred after about five minutes. The animal appeared suddenly to

"wake-up"--the reserpine syndrome was completely abolished and oculomotor coordination and spontaneous activity were fully restored. The effect of the stimulant wore off after about six hours, followed by the reappearance of many of the reserpine signs, such as absence of spontaneous activity and reassumption of the foetal position.

A comparable effect was reported in the study by Davis (1957). Reserpine (0.25 mg./kg.) was injected intramuscularly two hours before the start of activity testing in the photo-cell apparatus. Methylphenidate (10 mg./kg.) was administered subcutaneously ten min. prior to testing. By the time the Rhesus monkeys were put in the apparatus, the animals' lethargic state under reserpine had changed to the slightly agitated, alert condition typical of the effects of the stimulant drug alone. From the activity records of the subjects, the author was able to conclude that the effects of combination were not those of mutual neutralization, but rather were the exclusion of reserpine effects with exhibition of the effects of methylphenidate alone.

A slightly different interpretation of the interactive effects of methylphenidate and reserpine was reported by Dalrymple and Stretch (1967, in preparation). Rats trained on a tandem FI 4 min. FR 30 schedule of positive reinforcement underwent a series of drug tests, the final of which involved the effects of methylphenidate and reserpine acting simultaneously. Methylphenidate at dosages of 2.5 mg., 5 mg., and 10 mg./kg. was administered (i.p.) against a daily reserpine injection (i.p.) of 0.2 mg./kg. The authors' prime conclusion was that methylphenidate did not abolish the behavioral effects of reserpine (as concluded in the studies cited above) but rather, the methylphenidate behavior pattern, characteristic of that drug alone, was

apparent, but on a reduced scale, when the two drugs were administered in combination. Dalrymple & Stretch pointed out that in order for this interaction to be adequately characterized, the consideration of a number of factors, especially dosage levels of the two drugs and non-drug control rate of responding, is required.

An important study by Smith (1964) is illustrative of the types of effects produced on fixed-interval and fixed-ratio behavior by reserpine and a psychomotor stimulant administered in combination. Pigeons were trained on a multiple FI 5 min. FR 33 schedule of reinforcement. During drug tests, intramuscular injections of reserpine (0.1 mg./kg.) were made daily, 16 to 18 hours prior to the experimental session; d-Amphetamine was injected intramuscularly 5 minutes before the start of each session.

The FI 5 min. component generated characteristic fixed-interval behavior. The effect of d-Amphetamine alone depended on the initial control rate of responding. It markedly increased the low rates of responding characteristic of the first 60 seconds and suppressed the high rates of responding characteristic of the last 60 seconds. Reserpine alone greatly suppressed overall rates of responding. Small doses of d-Amphetamine restored normal rates and patterns of responding in reserpine-treated pigeons; and larger doses caused increases in rates which far surpassed rate increases attained in pigeons not treated with reserpine, "indicating a marked enhancement of the rate-increasing effect of d-Amphetamine by reserpine pretreatment." The mechanism was this--reserpine enhanced the rate-increasing effects of d-Amphetamine seen during the first 60 seconds and antagonized the rate suppressant effects seen during the last 60 seconds.

The FR 33 component also generated characteristic behavior. d-Amphetamine at 3 mg./kg., which produced the maximal increase in response rate during the FI 5 min. component, produced a significant decrease in fixed-ratio responding; reserpine tended to increase the duration of post-reinforcement pausing but overall had only a slight effect on fixed-ratio rates. In combination, d-Amphetamine eliminated pausing by reserpine-treated pigeons at the beginning of the FR 33 component, and reserpine antagonized the rate-suppressant effects of d-Amphetamine.

In summary, then, there was an increase after reserpine in the maximal overall rates of responding attained with d-Amphetamine in both schedule components, a finding that Smith interpreted as being "due to both an enhancement of the rate-increasing effects and an antagonism of the rate-suppressant effects of d-Amphetamine." Other drugs, specifically cocaine, pipradrol and imipramine were more effective than d-Amphetamine in increasing rates of responding of normal control pigeons and much less effective in increasing response rates of reserpine-treated pigeons. "Therefore reserpine did not cause a nonspecific enhancement of all drugs which increased rates of responding." Though Smith was cautious in the interpretation of these effects, his experiment is a very clear demonstration of the influence of environmental variables in determining the manner in which a given drug will modify given behavior patterns.

To conclude this section of the review, the literature indicates in general that the behavioral suppression induced by reserpine is in some way greatly attenuated by psychomotor stimulants.

The preceding review has been, of necessity, highly selective, including only research findings which have a more or less immediate bearing on the present study. Though the pharmacological literature concerning the drugs used was not covered in detail, exhaustive reviews of the pharmacology of methylphenidate (Kreuger and McGrath, 1964) and reserpine (Schlittler and Plummer, 1964) are readily available.

METHOD

Subjects

Four young adult male squirrel monkeys (*Saimiri sciureus*) were used (W_1 , W_2 , W_3 and W_4). Throughout the study, all subjects were maintained at normal body weight (approximately 475-525 gms.) by ad libitum food and water in the home cage.

Apparatus

The apparatus consisted of a standard sound resistant conditioning chamber with an electrifiable grid floor. The chamber was not fitted with a restraining chair, so that subjects (Ss) had complete freedom of movement, within the confines of the chamber. Relay equipment and electronic timers automatically controlled the experimental contingencies. Behavior was recorded by a printout counter and a Gerbrands cumulative recorder; 10 digital counters recorded the total number of responses made, and shocks delivered, during an experimental session.

Procedure¹

(a) Initial Training.

The initial training procedure was identical for all Ss. Daily session length was two hours, consisting of:

(1) 15 three minute periods, during each of which the lever was retracted, the house light was on, masking noise (80 DB) was present, and five electric shocks (2 mA., 0.5 sec. duration) were delivered through the grid floor--never less than 10 seconds apart, with the shock pattern being changed daily; and

¹See Appendix I for complete daily records for all Ss.

(2) time-outs (TOs) (controlled by a tape programmer) of varying length, totalling 75 minutes, during which the house light and masking noise were off and no shocks were delivered.

(b) Bar Introduction.

With the commencement of the second phase of training, session length was increased to five hours and the lever was introduced into the experimental space. Each session began with a 30 second TO, following which the lever was introduced and the house light and masking noise (conditioned aversive stimulation; CAS) came on. The S then had 10 seconds in which to make one lever press (response) to avoid delivery of a shock (2 mA., 0.5 sec. duration).² Failure to make a lever press resulted in shock delivery every 10 seconds until a correct response, which earned S a 30 second TO, was made.

Each S had six sessions under these conditions. At the end of these sessions, three Ss were responding frequently, receiving only 1-2 shocks per hour. One S, W₂, responded only infrequently, receiving 30-40 shocks per hour, and thus failed to come under schedule control. As a result it was replaced by a naive animal, also called W₂. The training procedure for this new S was curtailed, due partly to equipment programming complexities and partly to time considerations, i.e., to allow W₂ to quickly reach the level of proficiency of the other Ss. Consequently, the "Initial Training" procedure outlined above was eliminated, and W₂ began, in effect, with phase two, "Bar Introduction".

²Throughout training the shock intensity was increased in a step-like manner, so that by the time the final parameters were reached, shock intensity was 12 mA.

(c) Transition to Final Parameters.

The third phase of the training procedure involved the introduction of W_1 and W_2 to the fixed ratio (FR), and W_3 and W_4 to the fixed interval (FI), schedules of reinforcement. These developments will be discussed in turn.

(1) An FR schedule of reinforcement was defined in the Introduction. In order to establish FR 250, Ss were gradually shaped through a number of stages. That is, from session to session the FR requirement was either held constant or increased (usually by 5 or 10 responses), such increases being accompanied by commensurate increases in the light onset-shock interval (S_1 - S_2 interval) and the length of the T0. Sessions 6-12³ for W_2 demonstrate such stages:

<u>Session</u>	<u>Parameters</u>
6	FR 10 S_1 - S_2 10 TO 30
7	FR 15 S_1 - S_2 10 TO 30
8	FR 25 S_1 - S_2 20 TO 30
9	FR 30 S_1 - S_2 20 TO 30
10	FR 45 S_1 - S_2 35 TO 35
11	FR 50 S_1 - S_2 35 TO 35
12	FR 55 S_1 - S_2 40 TO 40

(As is apparent from the daily records of W_1 and W_2 [see Appendix Ia, b], the progress towards the final parameters was not entirely regular or uniform, to the point that either reductions in the FR requirement, or days in which the Ss were not tested, were necessitated occasionally in order to minimize the behavioral strain induced by the high ratio requirement.)

³from Appendix Ib.

Over a period of four months the following conditions were established: W_1 and W_2 were required to make 250 responses (FR 250) to terminate conditioned aversive stimulation for a period of three minutes, during which time the response lever was retracted and no shocks were possible. If the animals failed to meet the FR requirement within 180 seconds (S_1 - S_2 interval) timed from CAS onset, an electric shock (0.5 sec., 12 mA.) was delivered and then repeated at three minute intervals until completion of the FR requirement. Thus CAS could always be terminated prior to shock delivery (and shock avoided) providing 250 responses were made within the S_1 - S_2 interval of 180 seconds.

(2) A fixed-interval schedule of reinforcement, with a limited hold (LH) contingency operative, was defined in the Introduction. In establishing such a schedule in the present study, W_3 and W_4 advanced in stages, beginning at FI 30 LH 10 TO 30 (see Appendix Ic, d). As with the ratio animals, the progression was not without irregularity or interruption due to schedule-induced behavioral strain. The final parameters for W_3 and W_4 were FI 180 LH 2 TO 180, i.e., after CAS onset, responses were ineffective in terminating these stimuli until 180 seconds had elapsed; the first response to occur after this time terminated noise and light for a 180 second period which was accompanied by lever retraction. If the animals failed to make a response within two seconds (LH 2) at the end of the FI, a shock (0.5 sec., 12 mA.) occurred and was repeated every two seconds until a response was made. Thus CAS could always be terminated prior to shock delivery (and shock avoided) providing a response was made during a period of two seconds, preceding shock, which occurred three minutes after onset of CAS.

With attainment of the final parameters by all Ss, session length was reduced to 225 minutes, i.e., five 45 minute periods. Approximately 30-35 further sessions were given to ensure stability of control performances, as determined by visual inspection of the cumulative records,⁴ and comparisons of session shock and response totals.

(d) Psychopharmacological Manipulations.

Since subsequent procedures were different for each animal, the following description will deal with subjects individually.

(1) W₁. Upon stabilization at the final parameters, W₁ entered the phase dealing with the effects of methylphenidate on the ratio behavior. Methylphenidate⁵ at dosage levels of 1 mg./Kg., 2 mg./Kg. and 4 mg./Kg. was injected intraperitoneally one minute before commencement of a daily session. Five determinations of the effects of each dosage level were obtained in a random order, on separate occasions interspersed with control sessions. Methylphenidate control sessions, for all four Ss, were run without control injections. This was possible when examination of the Ss' behavior over the last 10 stabilization sessions (visual inspection of cumulative records and comparison of session response totals), at least three of which included saline injections immediately prior to the session, showed negligible differences between injection and non-injection sessions.

⁴A full discussion of the problems associated with behavioral stability and their criteria is found in Tactics of Scientific Research, by Murray Sidman (1960).

⁵The lyophilized hydrochloride salt of this drug dissolved in distilled water; Ciba trade name Ritalin.

After completion of this Dose-Effect series, W_1 received 10 restabilization sessions at reduced parameters--FR 50 S_1 - S_2 60 TO 60.⁶ Following restabilization, the above methylphenidate series was repeated at these new parameters.

(2) W_2 and W_3 . Upon stabilization at the final parameters, the effects of methylphenidate on ratio behavior and interval behavior were studied in W_2 and W_3 respectively, in exactly the same manner as with W_1 .

For W_2 , completion of this Dose-Effect series was followed by 10 restabilization sessions at reduced parameters--FR 100 S_1 - S_2 120 TO 120.

The final phase of the study was a series of methylphenidate Time Course determinations--at the reduced parameters for W_2 and the final parameters for W_3 . Methylphenidate at dosage levels of 1 mg./Kg., 2 mg./Kg. and 4 mg./Kg. was injected intraperitoneally either 90 or 180 minutes prior to the start of the experimental session (the animal being returned to the home cage until commencement of the session). Three determinations were made, at random, at each dosage-time combination--a total of 18 determinations; drug sessions were interspersed with control sessions, saline injections being made either 90 or 180 minutes before the start of each session.

(3) W_4 . The first phase of drug tests for W_4 was a methylphenidate Dose-Effect sequence identical to those of W_1 , W_2 and W_3 .

Immediately following completion of this series, W_4 sustained a simple fracture of both the radius and ulna of the left arm, necessitating four weeks of convalescence with the animal in a separate cage, plus a fifth week with the cast removed and the animal back in the home cage.

⁶For both W_1 and W_2 , the parameters were reduced in order to minimize the effects of ratio-strain.

At the end of the recuperative period, W_4 received five restabilization sessions at the final parameters, prior to the beginning of daily intraperitoneal administrations of reserpine.⁷ The restabilization sessions were used as the baseline for evaluating the degree of the reduction in behavior produced by reserpine.

In order to partially reduce the interval behavior, W_4 was injected intraperitoneally with reserpine, immediately post-session, according to the following schedule:

<u>Dosage Level</u> ⁸	<u>Number of Sessions Spent at Each Level</u>
.05 mg./Kg.	4
.1 mg./Kg.	3
.2 mg./Kg.	6
.3 mg./Kg.	10

Following establishment of the behavioral reduction, the experiment entered the final phase--the effects of methylphenidate and reserpine in combination. The daily post-session administrations of reserpine (.3 mg./Kg.) were continued, and methylphenidate was administered immediately pre-session, as follows:

⁷Dissolved in 1% benzyl alcohol and distilled water; Ciba trade name Serpasil.

⁸Increases in dosage level were determined on the basis of visual inspection of cumulative records and comparisons of session response totals.

<u>Sessions</u>	<u>Drug Administrations</u> ⁹
1-5	.3 mg./Kg. reserpine; 2 mg./Kg. methylphenidate
6-10	.3 mg./Kg. reserpine
11-15	.3 mg./Kg. reserpine; 4 mg./Kg. methylphenidate
16-20	.3 mg./Kg. reserpine

This concludes the description of the experimental manipulations involved in the study.

In addition to the cumulative record, performance on the FR 250 and FI 3 min. schedules of reinforcement was recorded by means of a print-out counter. Two measures were obtained from the latter:

(1) Duration of post-reinforcement pausing, defined as the time in seconds elapsing between CAS onset and the first response following that onset.

(2) Number of responses occurring in each of the six 30 second subdivisions comprising the three minute interval between CAS onset and delivery of the first shock.

Data obtained from each ratio or interval was presented as a number associated with one of the six successive thirty-second subdivisions, only during the first, third and fifth 45 minute period of a session.

In addition, a further measure was employed--the mathematical index of curvature for interval behavior developed by Fry, Kelleher and

⁹The 1 mg./Kg. dosage level of methylphenidate was not employed since it appeared from the methylphenidate Dose-Effect phase that the influence of this low dosage would not be sufficiently effective to produce a significant change in the behavioral output of W_4 .

Cook (1960)--with which it was possible to determine general trends and detailed effects from examination of the individual performances of W_3 and W_4 . In calculating mean indices of curvature, the first five intervals in each of the third and fifth periods were used, while intervals 2-6 were used from the first period (the first interval being eliminated to avoid any influence of warm-up effects¹⁰), a total of fifteen indices per session. Mean indices for drug treatments thus represent (15 X 5 sessions=) 75 indices, while for control conditions (15 X 10=) 150 indices comprise the mean.

¹⁰ A full discussion on exclusion of data is found in Chapters 8 and 9 of Tactics of Scientific Research, by Murray Sidman (1960).

RESULTS

The material to be presented in this section was derived from two sources: (1) Visual inspection of the cumulative records, revealing general trends which will be reported in terms of the stabilized baseline behavior patterns exhibited by individual subjects; and (2) Detailed findings emerging from analysis of the four categories of the print-out data: (a) response rate per minute, (b) shock rate per hour, (c) duration of post-reinforcement pausing, and (d) fixed-interval indices of curvature.

It should be noted that there were often wide individual differences between subjects in terms of the schedule of reinforcement employed. For this reason, and because of a high degree of intra-subject behavioral stability, the results are most meaningful when interpreted in terms of individual subjects. However, certain overall trends were also apparent following comparisons of the results of all subjects.

Though there was a certain amount of procedural replication (as was indicated in the Method section), in effect a different experiment was carried out with each subject. Consequently in this section the results will be reported for each subject in turn, beginning with the ratio animals.

It was apparent even during the transition to the final ratio parameters that the performance of W_2 was more stable and less subject to ratio "strain" than was that of W_1 . To highlight this important difference it will be most beneficial to present first the results for W_2 , and then those of W_1 by way of comparison.

At the final parameters, W_2 exhibited characteristic fixed-ratio behavior, similar in all respects to that described by Ferster and Skinner

(Fig. 2). That is, reinforcement was followed by a substantial pause, after which the animal responded at a high and constant rate until the 250 responses had been made, and another reinforcement earned. This pattern, evident during both pre-drug stabilization sessions and non-drug control sessions, is apparent in Figure 3.

The effects of 1 mg./Kg. methylphenidate were straightforward, and in terms of the control baseline may be summarized as follows: a reduction in the duration of post-reinforcement pausing coupled with a decrease, followed by an slight increase in rate of responding engendered a high-output, almost shock-free performance (Figs. 4, 36 a, b; Table 1b).¹

More complex were the gross behavioral changes produced by the 2 mg./Kg. dosage. Both response rate and duration of post-reinforcement pausing were markedly abbreviated during the first half of the session (Fig. 5). Observation of the animal in the conditioning chamber revealed that the lowered response rate was a function of drug-induced hyperactivity in behavior (inattention to the lever and undue interest in long-familiar aspects of the experimental environment), and was sufficient to increase the frequency of shock delivery significantly over control levels (Table 1b). As drug action took its course, hyperactivity was gradually replaced by a less generalized excitation (close attention to the lever) which was marked by continued short pausing but a substantial increase in rate of responding, as evident again in Fig. 5.

Fig. 6 reveals that 4 mg./Kg. methylphenidate produced similar but more pronounced effects than the intermediate dosage. That is, the hyperactivity-induced depression of responding (and ensuing high shock frequency) persisted throughout most of the session, giving way to high-rate responding only towards the very end of the session.

¹For Figures 36-41 (histograms) see pp. 105-110; for Tables 1-3 see Appendix 2, pp. 169-171.

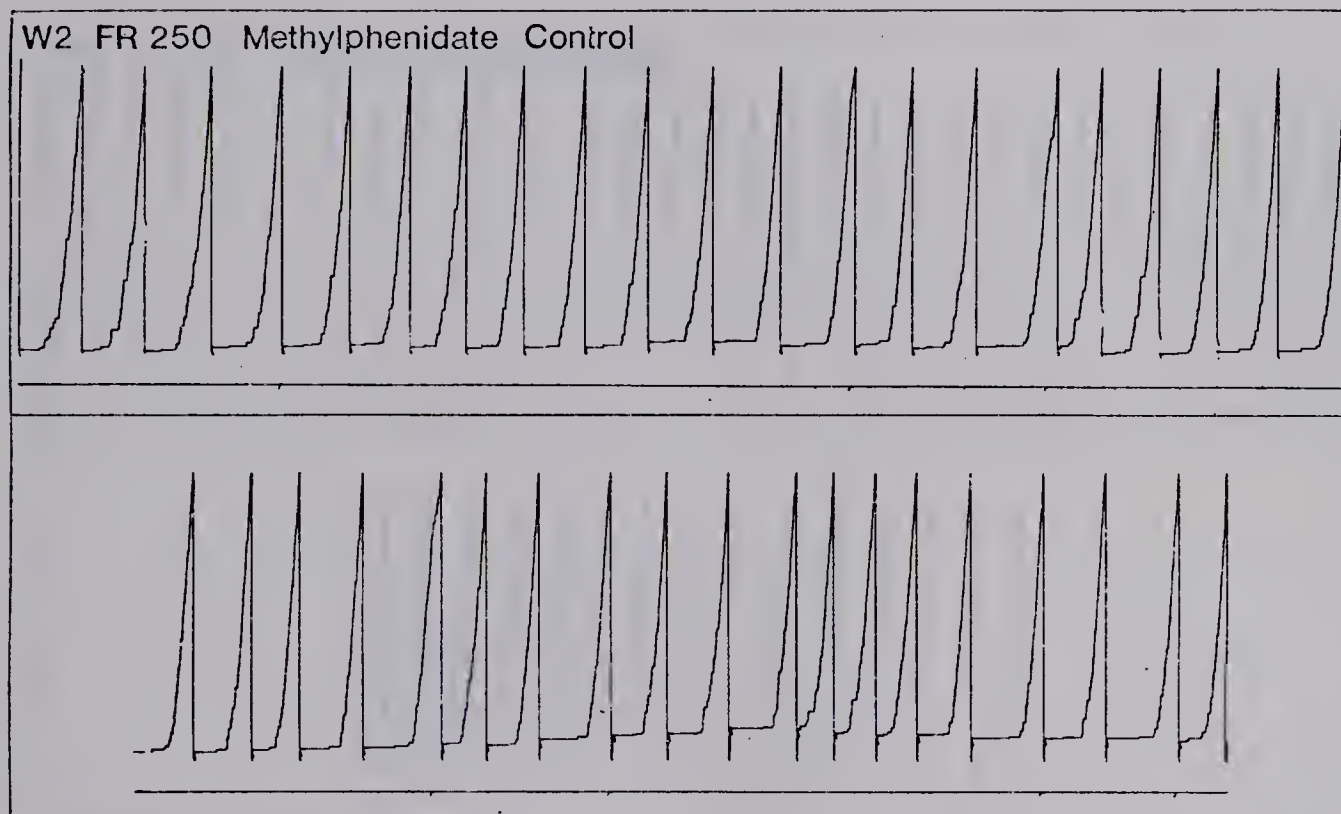


Fig. 3: W_2

Cumulative record of control performance on FR 250.

NOTE: For all figures of cumulative records: the short downward strokes of the recording pen indicate time-out periods in which the paper feed stopped; short downward strokes of the event pen indicate shock deliveries; the recording pen reset to the bottom of the record when 250 responses had cumulated, and at the end of each session; in Figures 3-6, 15-22 and 29-34 the upper and lower records in each figure are continuous, showing performance over an entire experimental session; in Figures 7-14 and 25-28 each upper and lower record is an entity unto itself, showing performance over approximately the first half of an experimental session. Time base for all figures: 1 inch = 20 minutes.

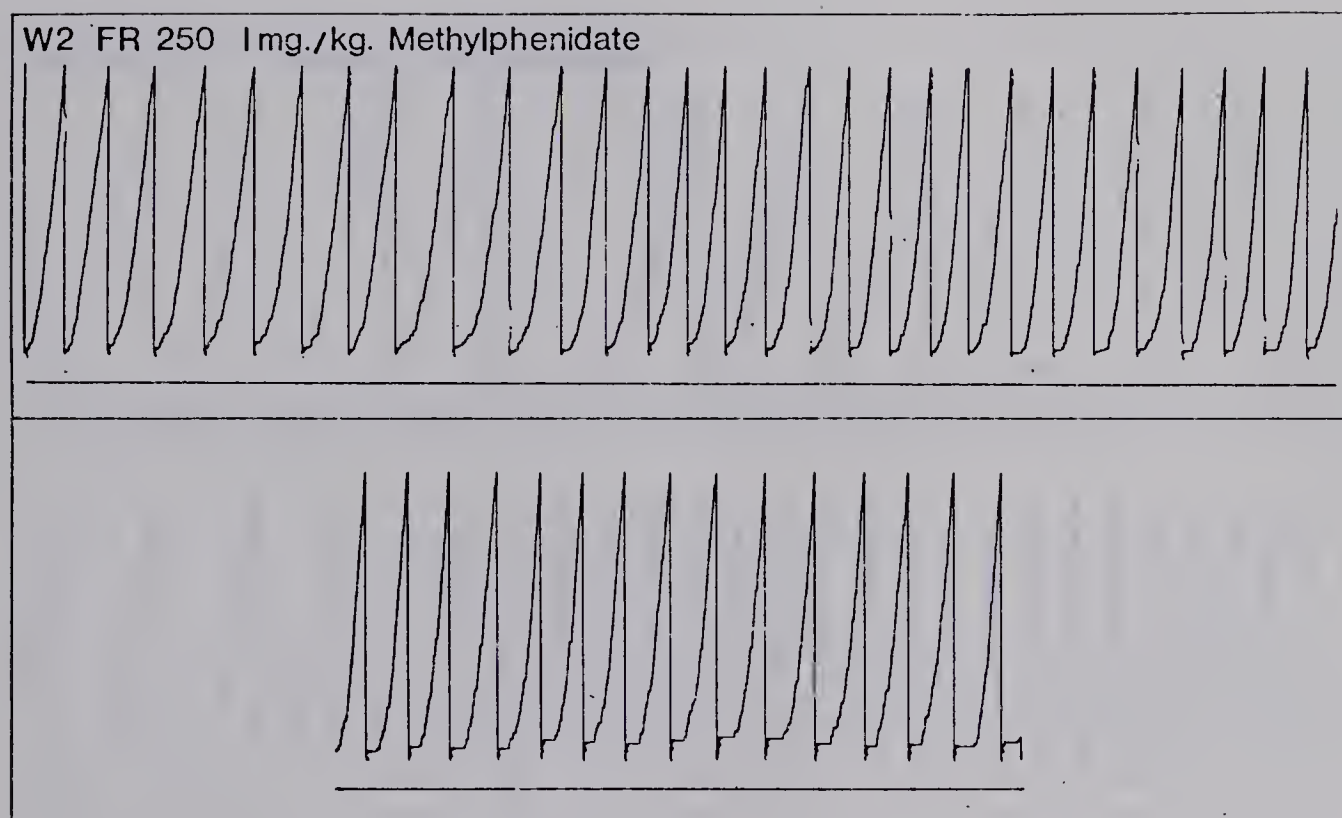


Fig. 4: W_2

Cumulative record of performance on FR 250 obtained following administration of 1 mg./Kg. Methylphenidate.

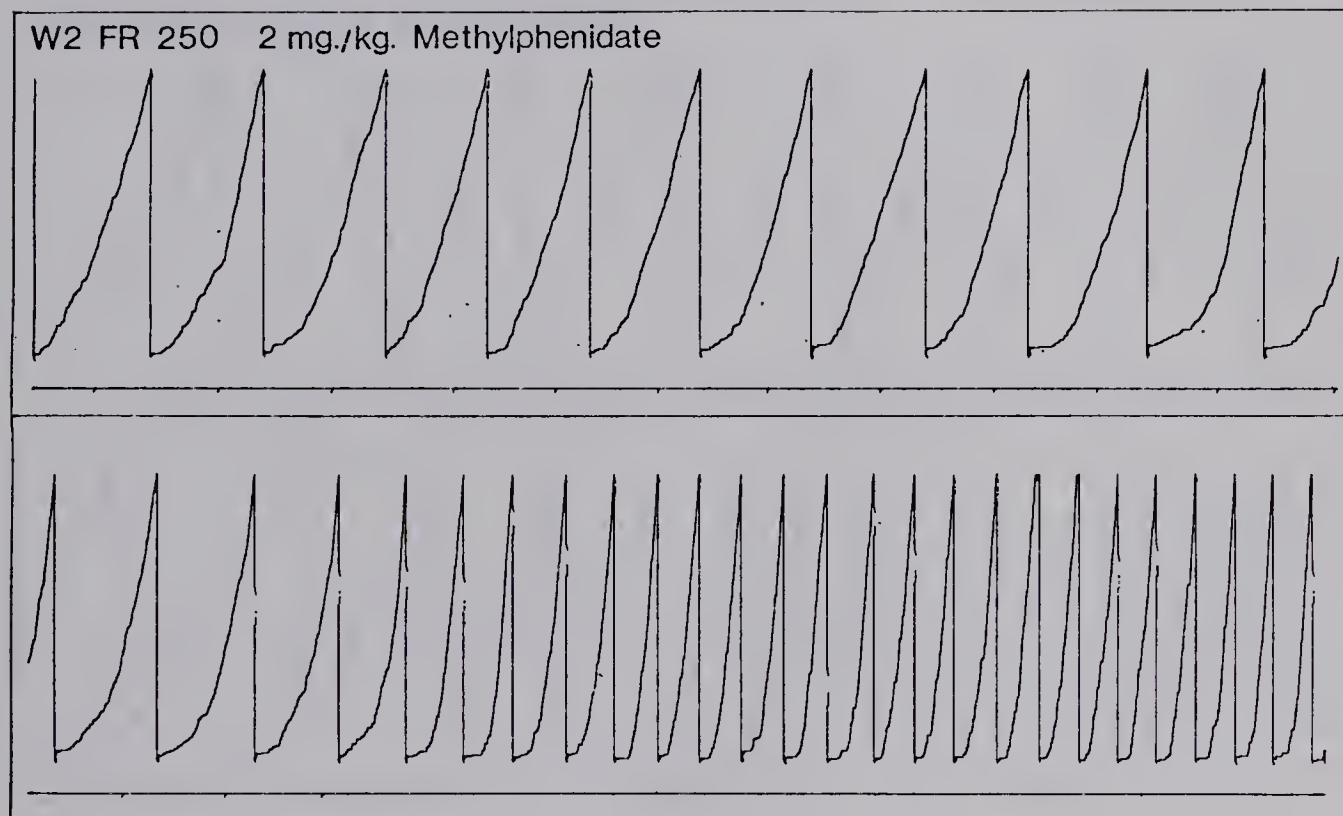


Fig. 5: W_2

Cumulative record of performance on FR 250 obtained following administration of 2 mg./Kg. Methylphenidate.

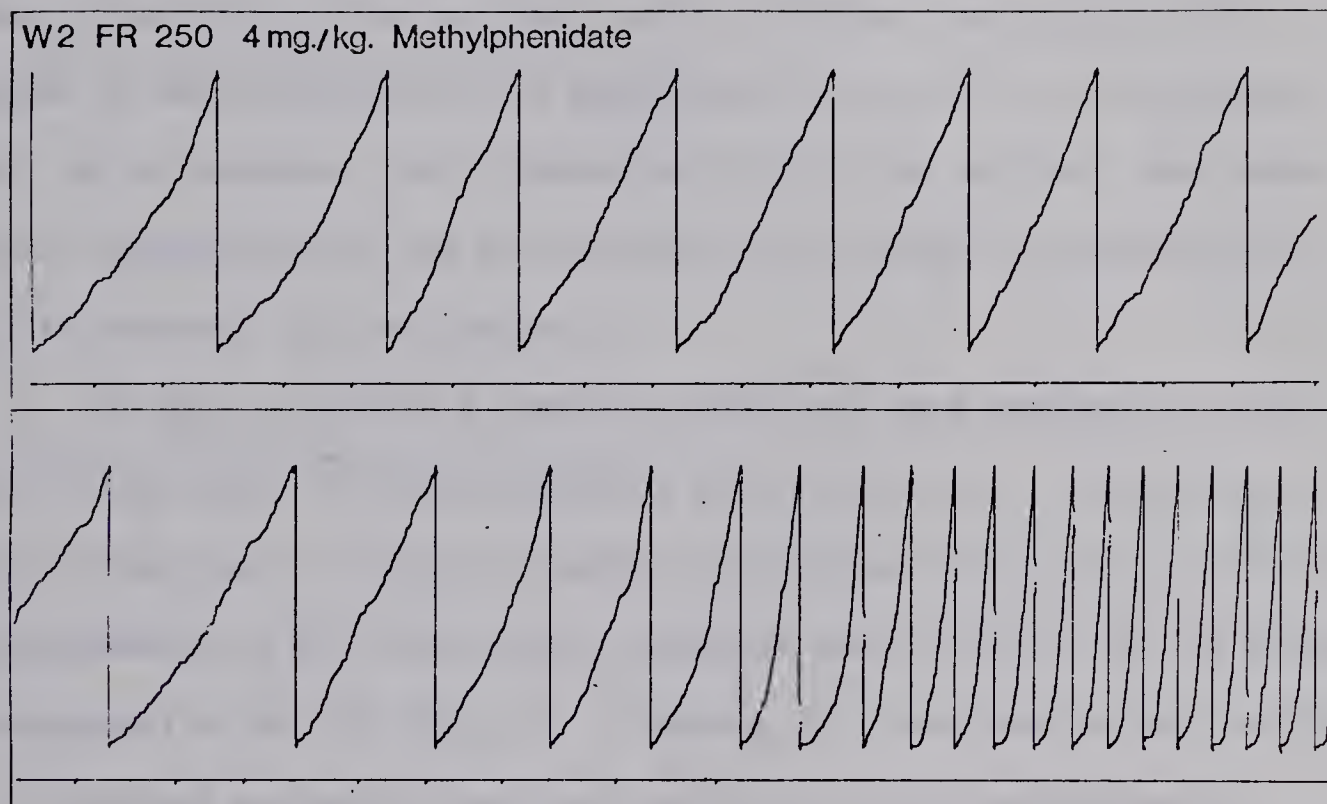


Fig. 6: W₂

Cumulative record of performance on FR 250 obtained following administration of 4 mg./Kg. Methylphenidate.

Obviously, the methylphenidate Dose-Effect curves described above were not the products of dosage level alone. It was apparent at all dosage levels that methylphenidate still exerted an appreciable influence on behavior even at the end of the experimental sessions. Consequently, at this point it is appropriate to review the findings of the Time Course phase of the study, that is, the results obtained from W_2 when the dosages of methylphenidate were administered either 90 or 180 minutes prior to the session. The findings will simply be outlined, and beyond certain comparisons to the above results, any attempt at interpretation will be reserved for the Discussion.

It will be recalled that the parameters were reduced for the Time Course series of methylphenidate administrations. Nevertheless, typical fixed-ratio behavior, similar in all respects to that at FR 250, was engendered in W_2 under saline injection conditions (90 or 180 minutes pre-session) by FR 100 (Fig. 7). (Because the behavioral output required by the reduced parameters was less, duration of post-reinforcement pausing was longer and response rate lower than at the original parameters.)

One mg./Kg. methylphenidate injected 90 minutes prior to the session (Fig. 8) had little or no effect on rate of responding or shock frequency, but did reduce duration of post-reinforcement pausing--by half during the first 45 minutes and to a lesser degree during the remainder of the session. Injected 180 minutes pre-session, the only effect of the low dosage was to produce a slight reduction in duration of post-reinforcement pausing.

In summary, both the Dose-Effect and Time Course phases of the experiment indicate that, beyond producing a slight response rate ^{decrease, then} increase

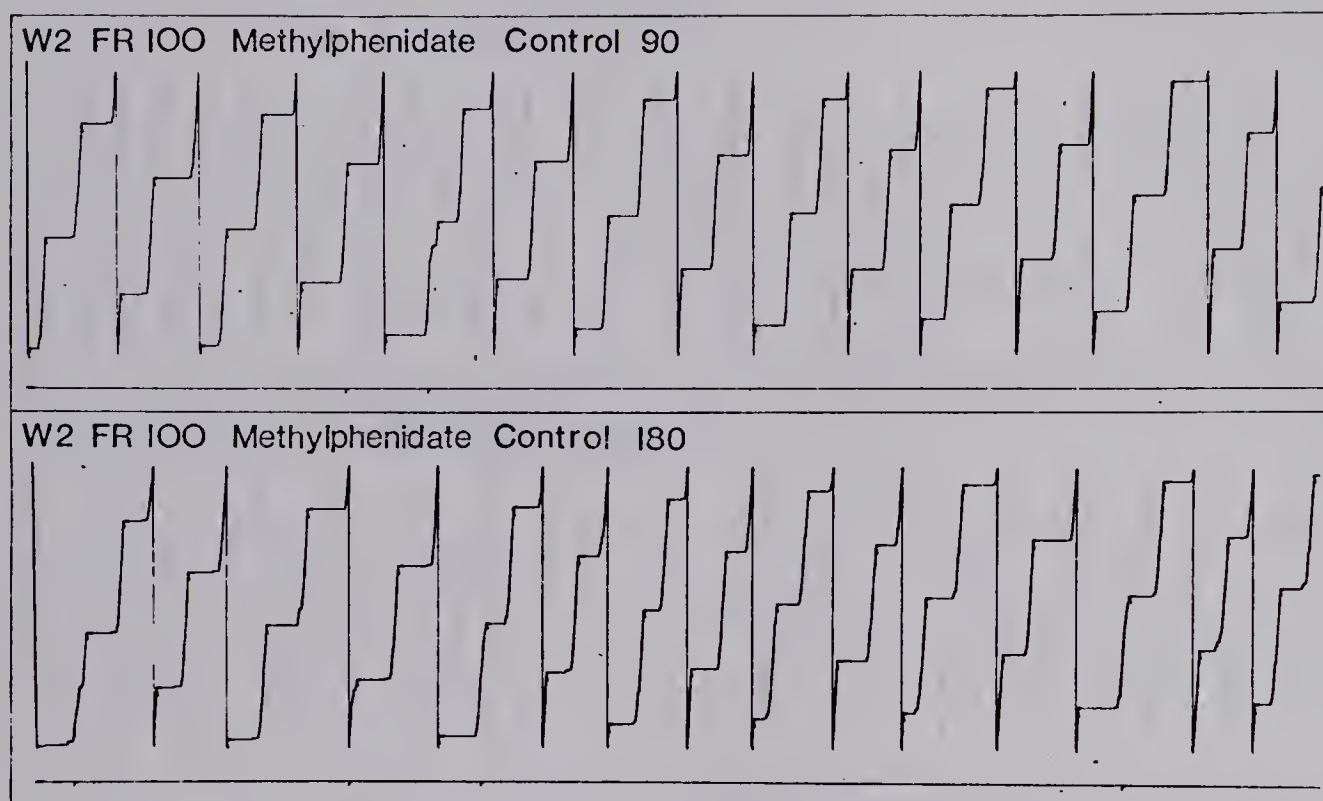


Fig. 7: W₂

Cumulative records of performance on FR 100 obtained following pre-session saline administrations.

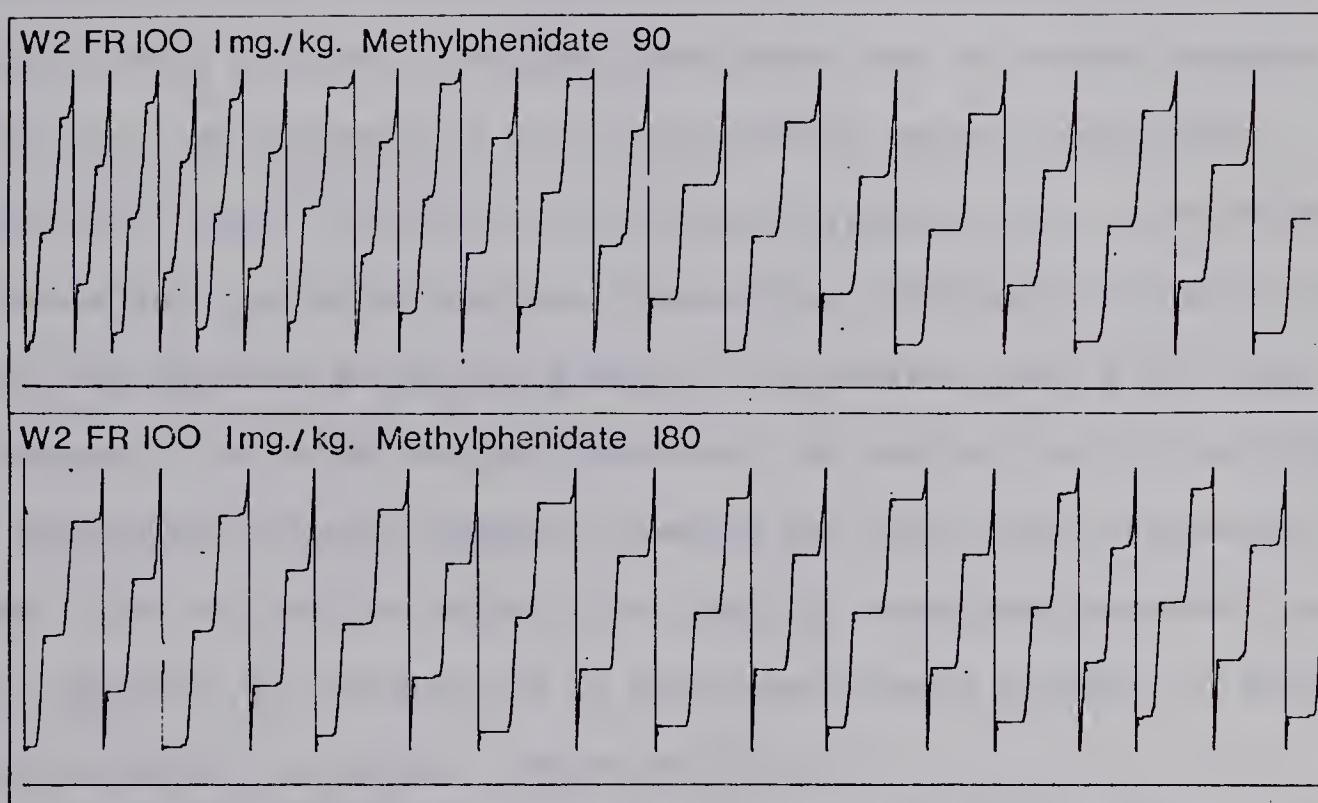


Fig. 8: W₂

Cumulative records of performance on FR 100 obtained following pre-session administrations of 1 mg./Kg. Methylphenidate.

at the start of a session, the chief effect of methylphenidate at 1 mg./Kg. appeared to be a long-lasting reduction in the duration of post-reinforcement pausing.

During the first 45 minutes of a 2 mg./Kg. methylphenidate--90 session, duration of post-reinforcement pausing was greatly reduced (Fig. 9); in addition, rate of responding underwent a marked decrease, with the overall result that shock frequency was double that of control sessions (Table 1b). As was the case in the Dose-Effect series, these gross behavioral changes were due to drug-induced hyperactivity in the subject. Following this period of depressed responding, behavioral excitation (as above) was apparent during the middle of the session, and by the final 45 minutes, drug action having diminished, the control rate of responding had reappeared, although length of pausing was still below the control level. The only obvious effect of a 2 mg./Kg. methylphenidate--180 dosage was a reduction in the duration of post-reinforcement pausing, an effect which was slight by session completion (Fig. 9).

Overall, the observable changes induced by 2 mg./Kg. methylphenidate, as observed in both phases of the study, comprised a stable three-phased behavioral sequence (depression-excitation-control), which was dependent on the time course of action of the drug.

Inspection of Fig. 10, that is, the effects of 4 mg./Kg. methylphenidate 90 and 180 minutes pre-session, again reveals this sequence of temporally-dependent behavior changes, and in addition indicates that, since only the control response rate baseline was beginning to reappear towards the end of a 4 mg./Kg.--180 session, the duration of drug effect at the high dosage was well in excess of six hours.

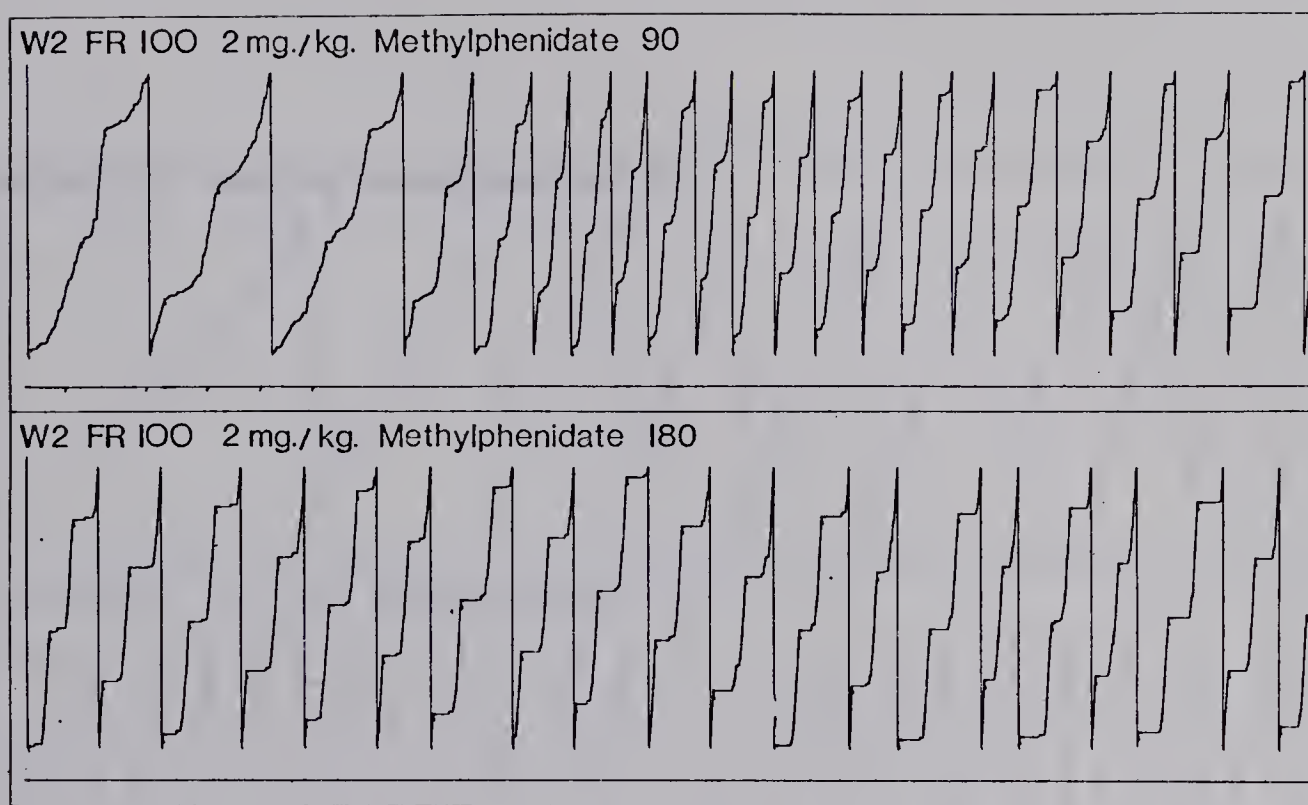


Fig. 9: W₂

Cumulative records of performance on FR 100 obtained following pre-session administrations of 2 mg./Kg. Methylphenidate.

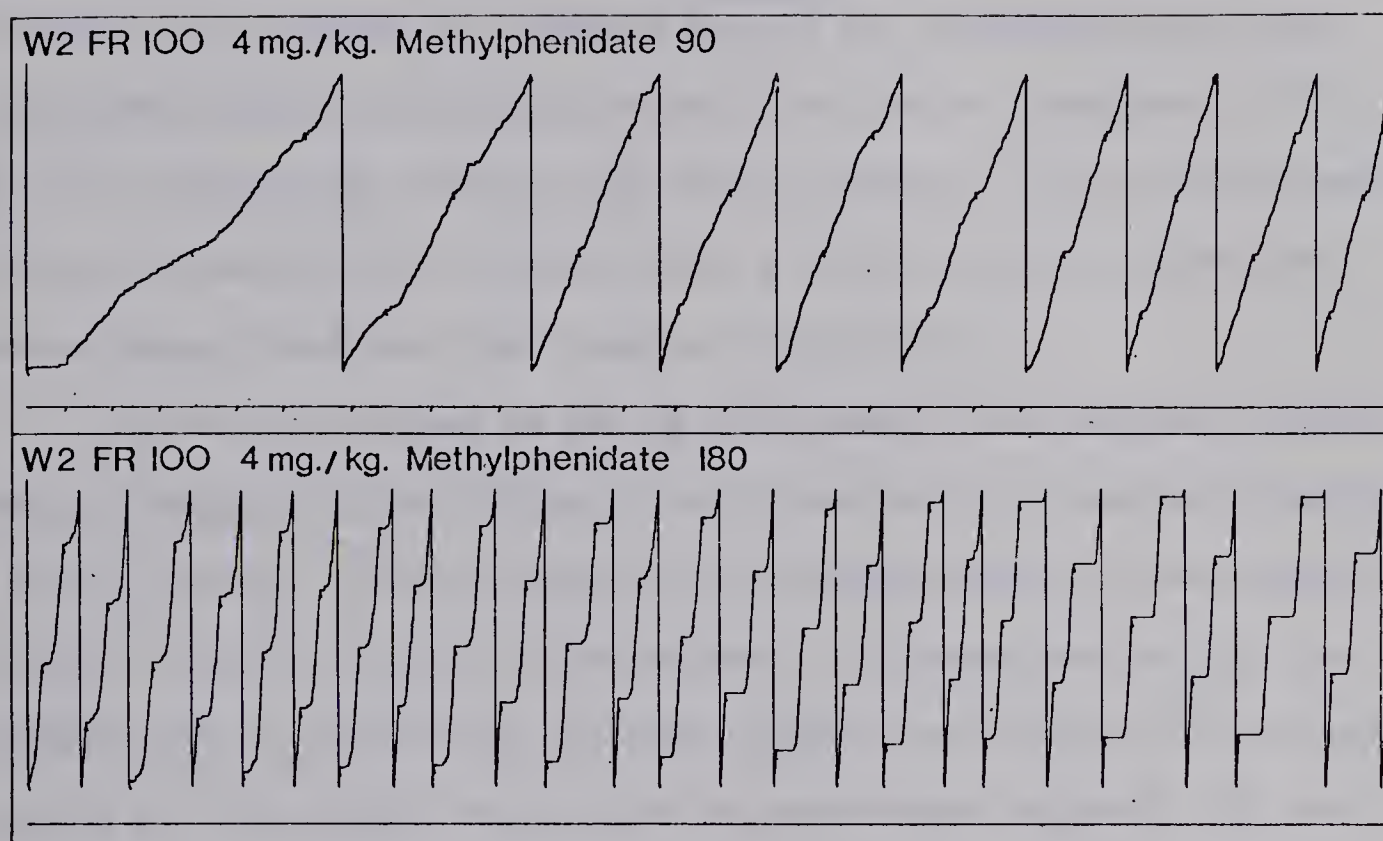


Fig. 10: W₂

Cumulative records of performance on FR 100 obtained following pre-session administrations of 4 mg./Kg. Methylphenidate.

In conclusion, the effects of 1, 2 and 4 mg./Kg. methylphenidate on the fixed-ratio behavior of W_2 may be summarized as follows: as compared with the control baseline, (1) a marked abbreviation in duration of post-reinforcement pausing at all dosage levels, (2) a substantial reduction of, followed by an increase in, response rate^{especially} at the intermediate and high dosage levels, and (3) a gradual reversion to control baselines of first the ratio (responding) behavior and second, duration of post-reinforcement pausing, the rapidity of reversion being a function of the interaction between dosage level and time course of drug action.

W_1 was also trained on the FR 250 schedule, the original intention being to demonstrate the effects of methylphenidate on fixed-ratio behavior in both W_1 and W_2 . From the outset of the study, however, it was apparent that this intention was not to be realized. In comparison with W_2 , the performance of W_1 , even during training sessions, was marked by (a) slower progress and (b) frequent disruptions in performance (Appendix 1a), and although W_1 did attain the final parameters, its performance at these parameters at no time displayed the degree of behavioral proficiency exhibited by W_2 ; in a phrase, the ratio behavior of W_1 was never under the same degree of "schedule control" as was the behavior of W_2 .

The dichotomy is well illustrated by a comparison of Figs. 11 and 3 which depict typical non-drug control performances on FR 250 of W_1 and W_2 respectively. The performance of W_2 , as described earlier, was the epitome of fixed-ratio behavior. In contrast, the behavior of W_1 can at best be characterized as atypical. The duration of post-reinforcement pausing was extremely variable, and protracted to the extent that three or four shocks (at the rate of one every three minutes)

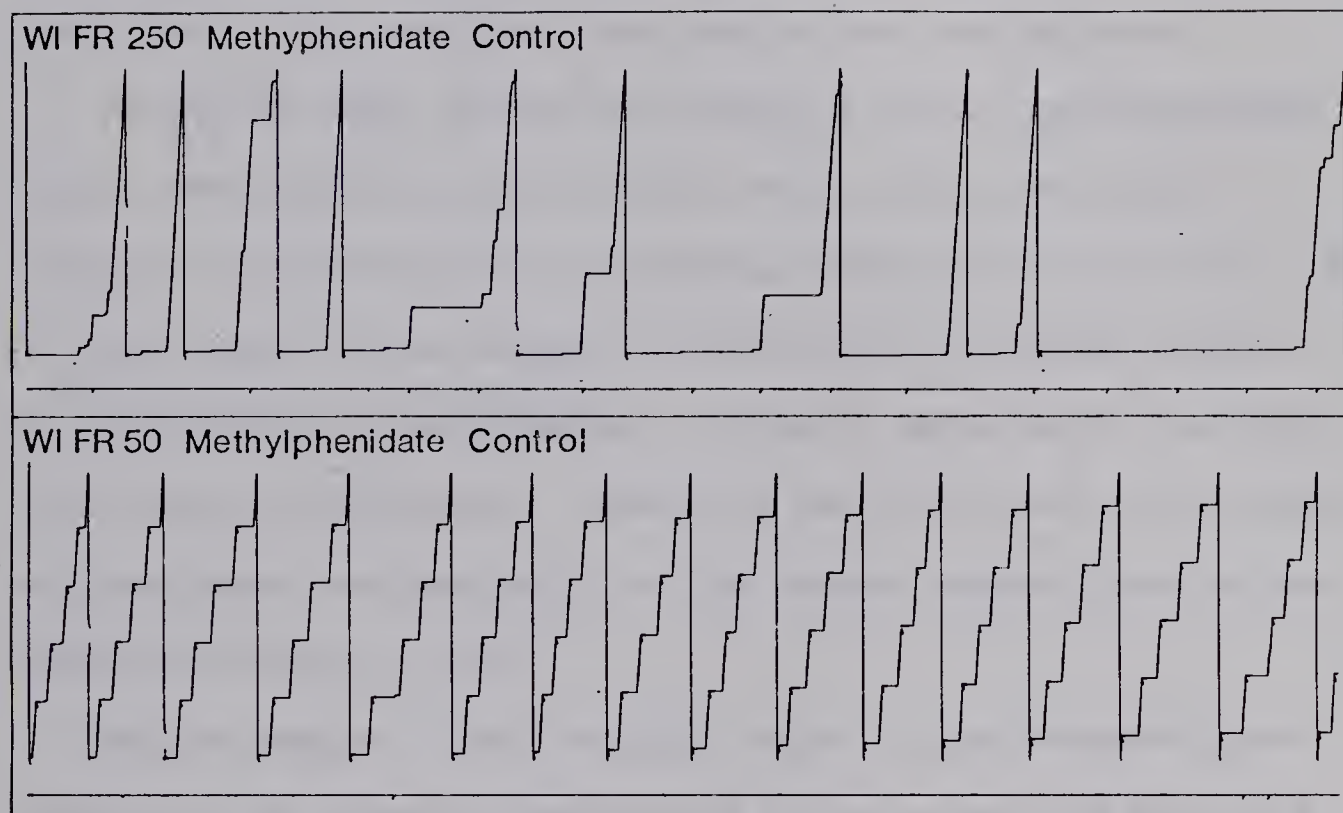


Fig. 11: W_1

Cumulative records of control performances on FR 250 and FR 50.

often occurred before the first response was made. Once responding began, the characteristic "ratio-run" to reinforcement was absent; instead, runs of responses of varying length occurred, often punctuated by long periods of no responding. Behavior under such a low degree of schedule control could be expected to undergo unpredictable changes under drug treatment, and this in fact was the case.

During the first part of the session, 1 mg./Kg. methylphenidate reduced the duration of post-reinforcement pausing and largely eliminated the periods of no responding during the ratio-run (Fig. 12). In other words, the low dosage was sufficient to somewhat enhance the weak control of the schedule, the result being fairly characteristic fixed-ratio behavior. However, by the latter half of the session the drug effect had dissipated and the erratic control baseline was reinstated (Figs. 37, 38).

Higher dosages (2 and 4 mg./Kg.; Figs. 13, 14) induced hyperactivity in the overall behavior of W_1 , just as they had done in W_2 . The combination of weak schedule control plus extremely agitated behavior engendered performances typified by long post-reinforcement pauses and response rates that were low and often interrupted by substantial periods of no responding, especially at the highest dosage level.

Such behavior could never be considered a reliable measure of drug effect. Consequently, when the Dose-Effect series had been completed at the high ratio requirement, W_1 was restabilized at FR 50, because it was felt that establishment of schedule control over

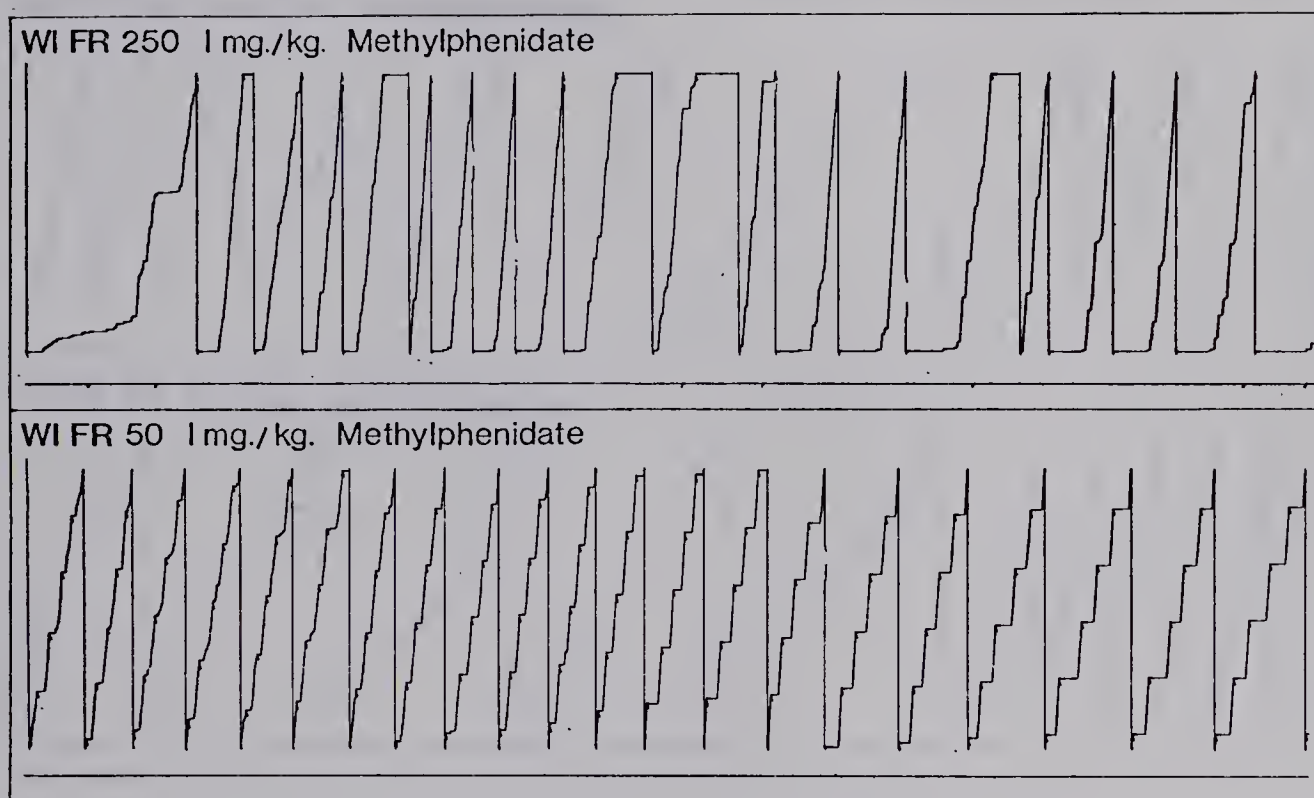


Fig. 12: W_1

Cumulative records of performance on FR 250 and FR 50 obtained following the administration of 1 mg./Kg. Methylphenidate.

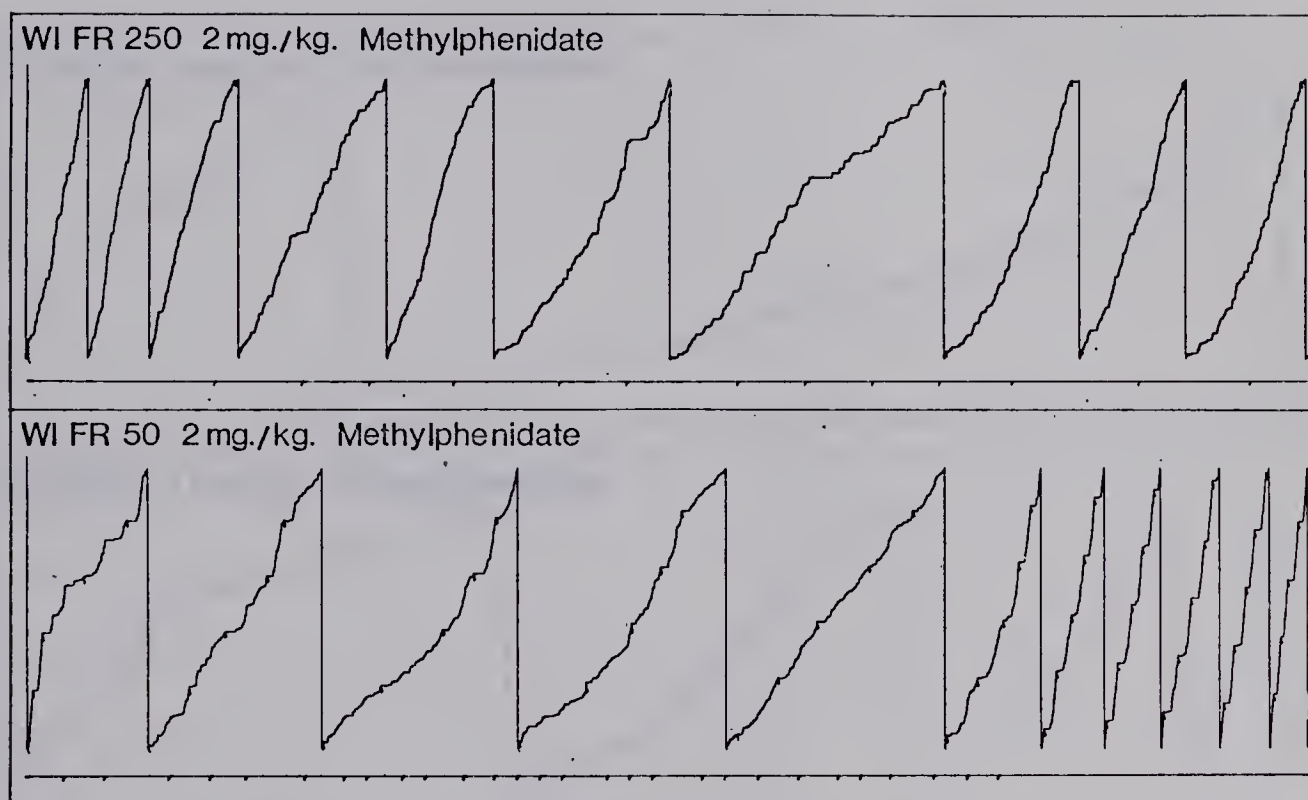


Fig. 13: W_1

Cumulative records of performance on FR 250 and FR 50 obtained following the administration of 2 mg./Kg. Methylphenidate.

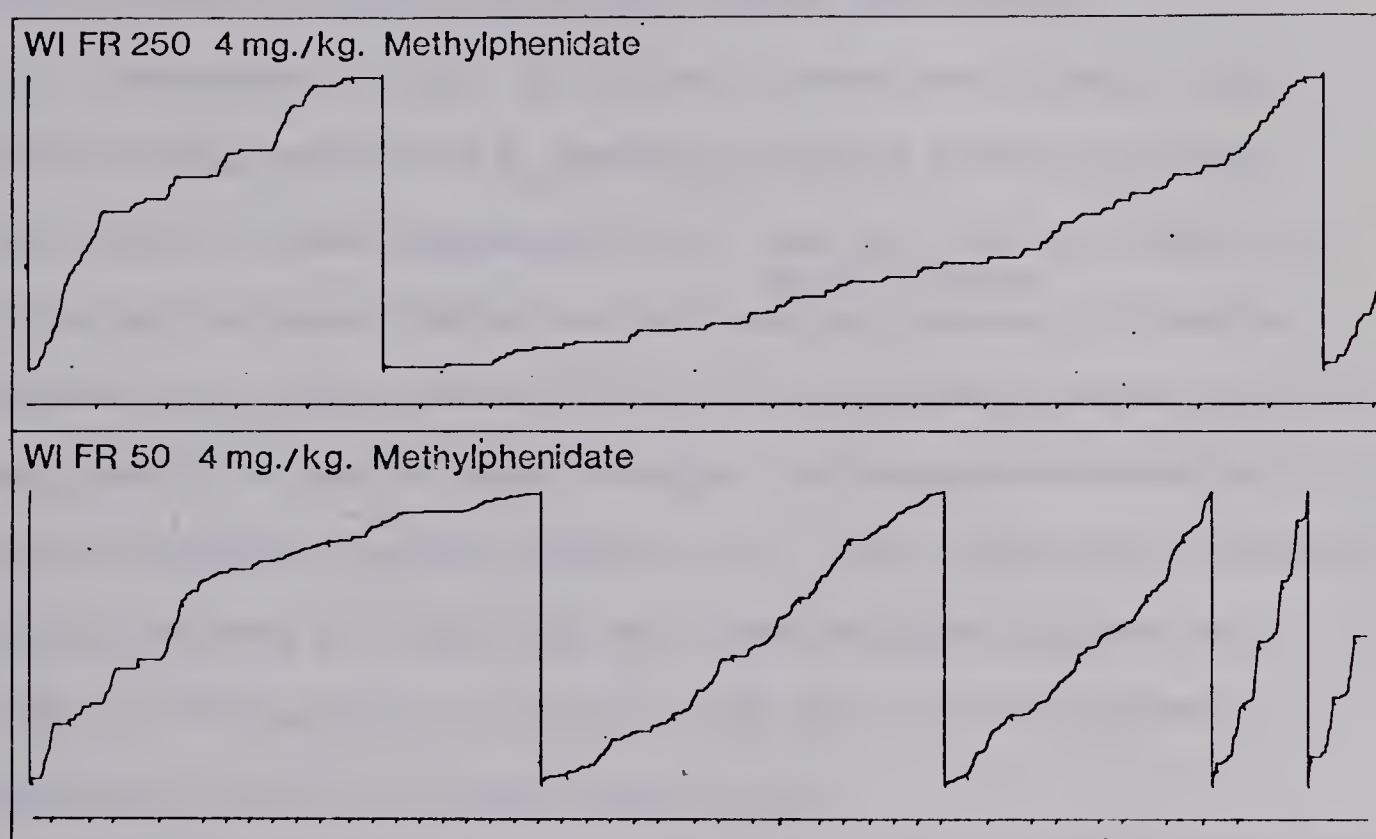


Fig. 14: W_1

Cumulative records of performance on FR 250 and FR 50 obtained following the administration of 4 mg./Kg. Methylphenidate.

behavior could be more readily achieved at these less stringent parameters.

The manipulation was successful, the new parameters giving rise to characteristic, highly stable fixed-ratio behavior (Fig. 11), against which the methylphenidate Dose-Effect series was repeated.

Inspection of Figs. 12, 13 and 14 shows that at each dosage level the drug produced in W_1 behavioral changes similar in almost every detail to those engendered in W_2 : that is, (a) at 1 mg./Kg., an initial mild stimulant effect due to a marginal ^{decrease, then an} increase, in response rate and a substantial reduction in duration of pausing after reinforcement; and (b) at the two higher dosages, the depression-excitation-control behavioral sequence observed in W_2 . The disruption of the FR 50 baseline behavior by 2 and 4 mg./Kg. methylphenidate was even more dramatic than that in W_2 at FR 250. This fact was not, however, surprising in view of the past history of W_1 .

The data obtained from W_1 and W_2 indicate, in summary, that the effect of methylphenidate on fixed-ratio behavior at the time of maximal drug action, especially at the higher dosages, was twofold: (1) generation of responding during the period which under control conditions was the post-reinforcement pause; and (2) depression of high-rate ratio run responding.

The results for the ratio animals having been dealt with, attention will now be focussed on the interval animals. A methylphenidate Dose-Effect series was carried out with both W_3 and W_4 ; therefore, their results may be considered together.

It was immediately apparent that the FI schedule engendered qualitatively different behaviors in the two animals. Compared to W_4 , W_3 on average made considerably more responses per reinforcement, characteristically pausing for about one-third of the interval, then responding at a relatively rapid, only moderately accelerated rate. On the other hand, during most inter-reinforcement intervals, W_4 paused for almost two-thirds of the interval, only then beginning to respond, in a highly accelerating fashion, until reinforcement was obtained. Figs. 15 and 16 illustrate these behavioral baselines, of which, if anything, that of W_4 is more typical of FI patterns of responding.

With such differences in control baselines, differential effects of methylphenidate on these baselines were predictably obtained, though less at the low dosage than the higher ones. Methylphenidate at 1 mg./kg. led to a marked diminution in the length^{of} post-reinforcement pausing in both animals, the effect being less marked and of shorter duration in W_4 than W_3 (Figs. 40b, 39b). With respect to response rate, on the other hand, though the drug engendered an increase in both subjects, the effect was more pronounced, in both magnitude and duration, on W_4 than W_3 (Figs. 40a, 39a). Overall, these effects of the low dosage were greatest during the first half of the session and were more apparent in W_4 than W_3 by session completion (Figs. 18, 17).

At the higher dosages, however, drug effect diminished more rapidly in W_4 than W_3 as shown by Figs. 20 and 19. The gross behavioral changes brought about in W_4 by 2 mg./Kg. methylphenidate were similar to those at 1 mg./Kg., as inspection of Fig. 40a, b, indicates, and need not be discussed further. With W_3 the

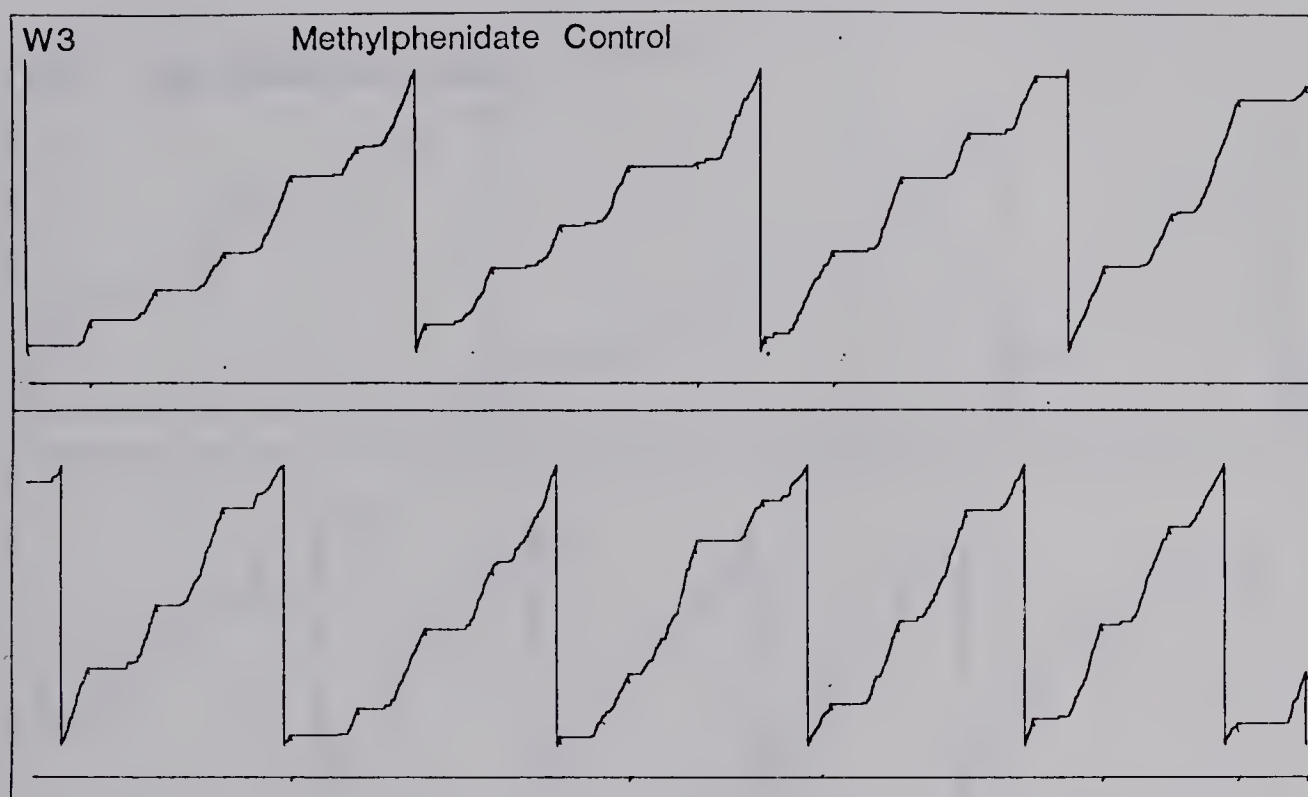


Fig. 15: W_3
Cumulative record of control performance on FI 180 LH 2.

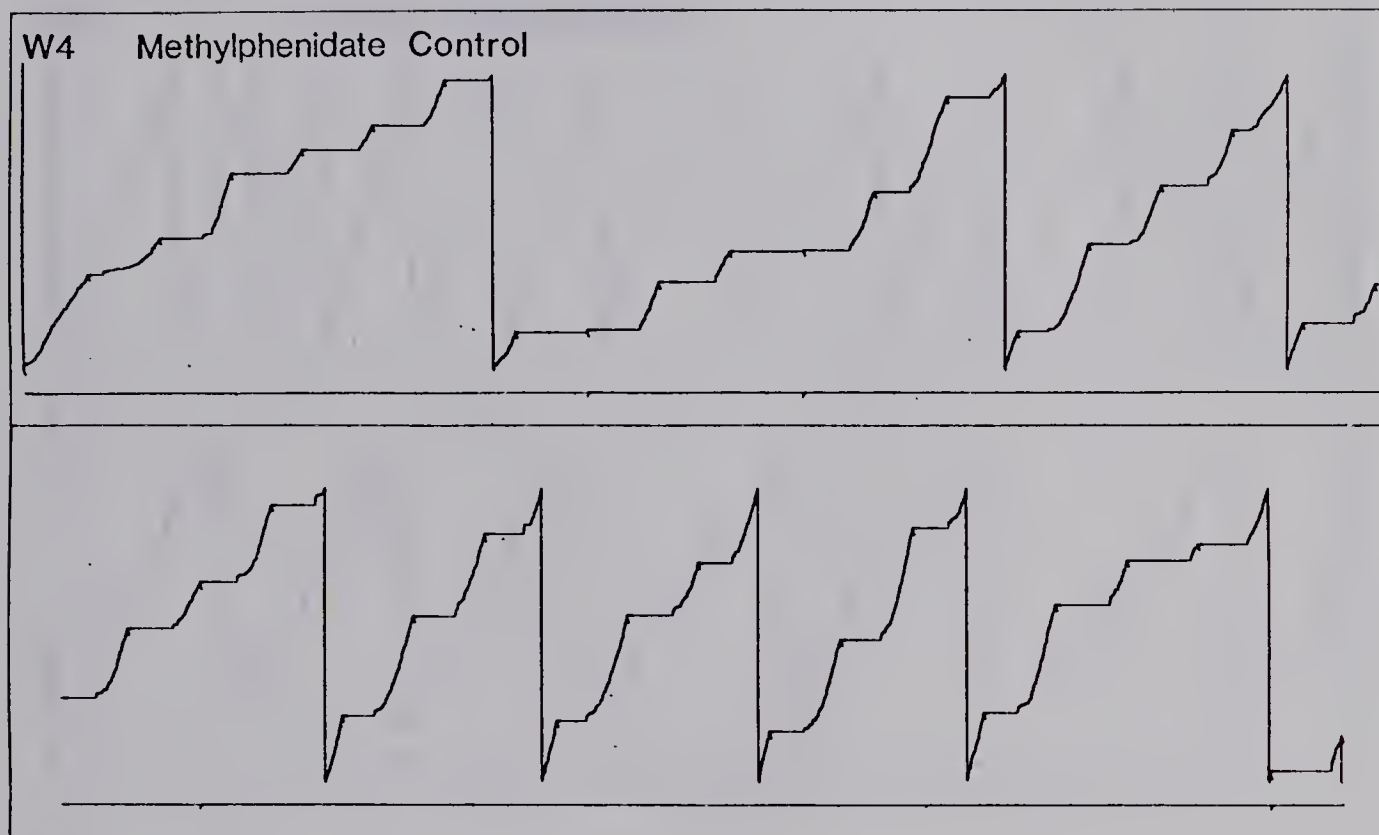


Fig. 16: W_4

Cumulative record of control performance on FI 180 LH 2.

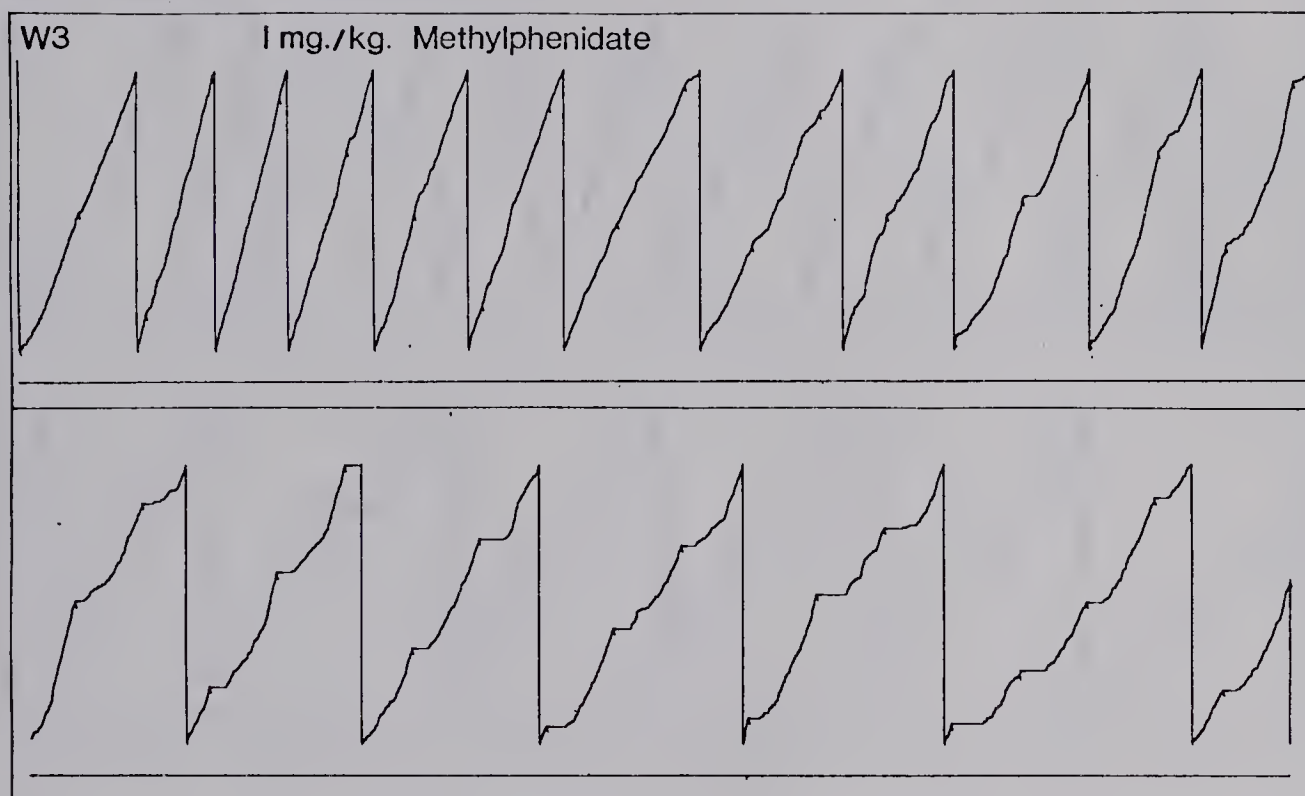


Fig. 17: W_3

Cumulative record of performance on FI 180 LH 2 obtained following administration of 1 mg./Kg. Methylphenidate.

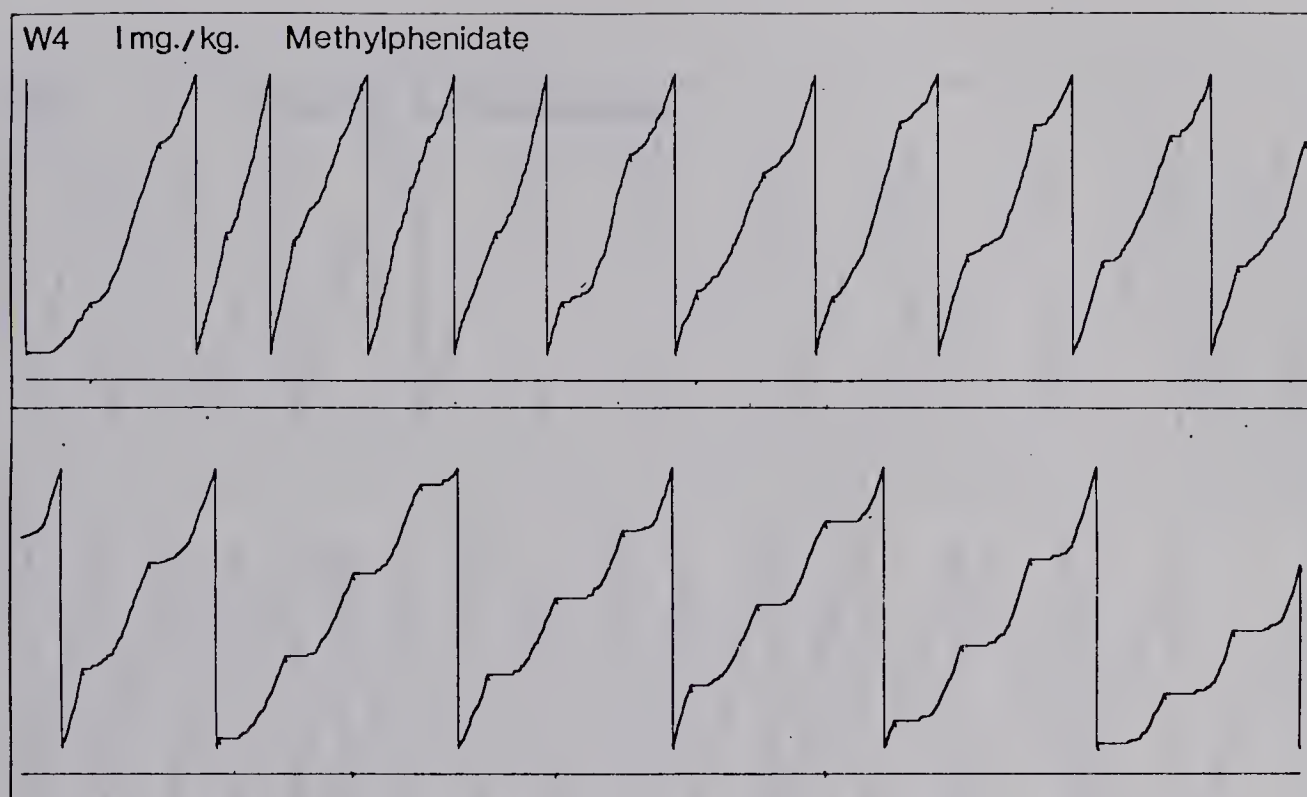


Fig. 18: W_4

Cumulative record of performance on FI 180 LH 2 obtained following administration of 1 mg./Kg. Methylphenidate.

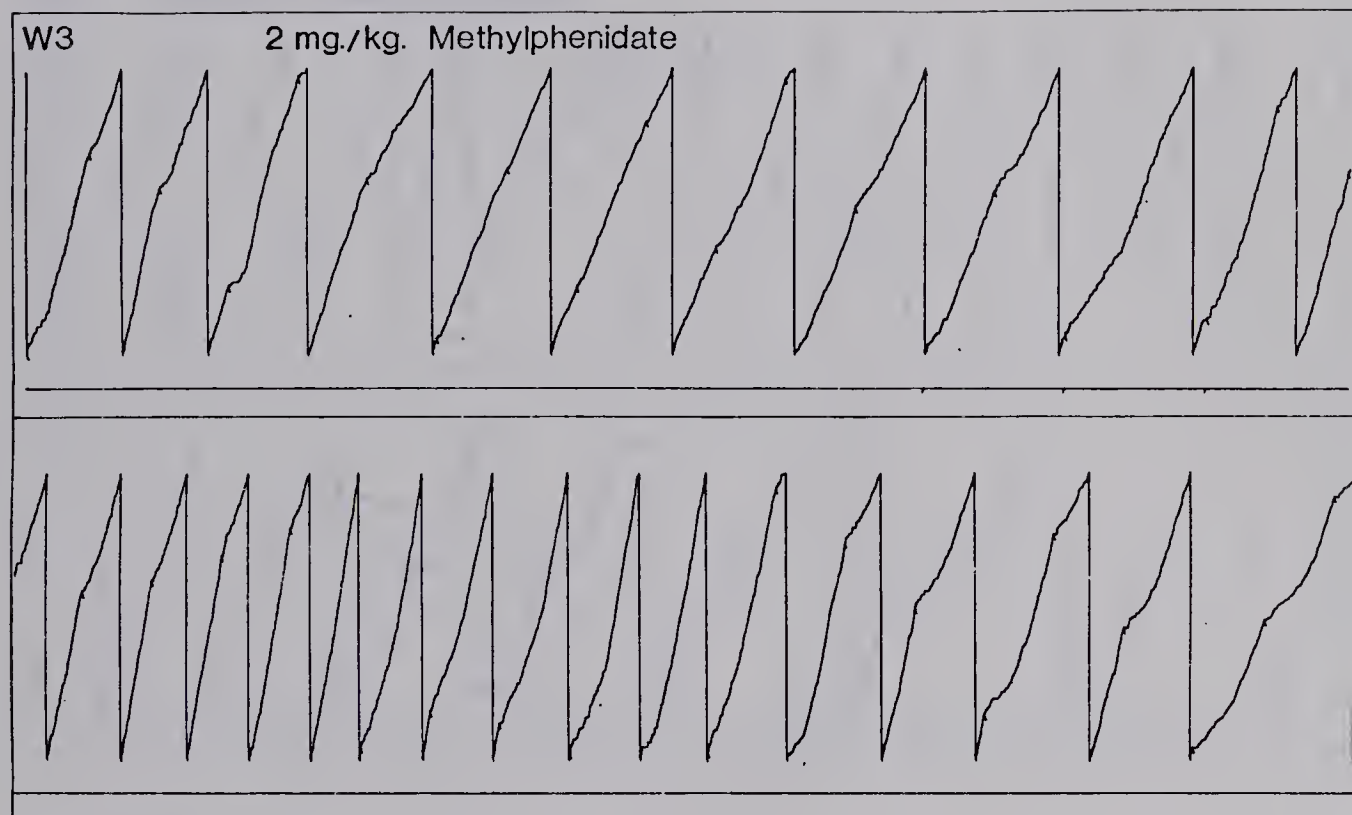


Fig. 19: W_3

Cumulative record of performance on FI 180 LH 2 obtained following administration of 2 mg./Kg. Methylphenidate.

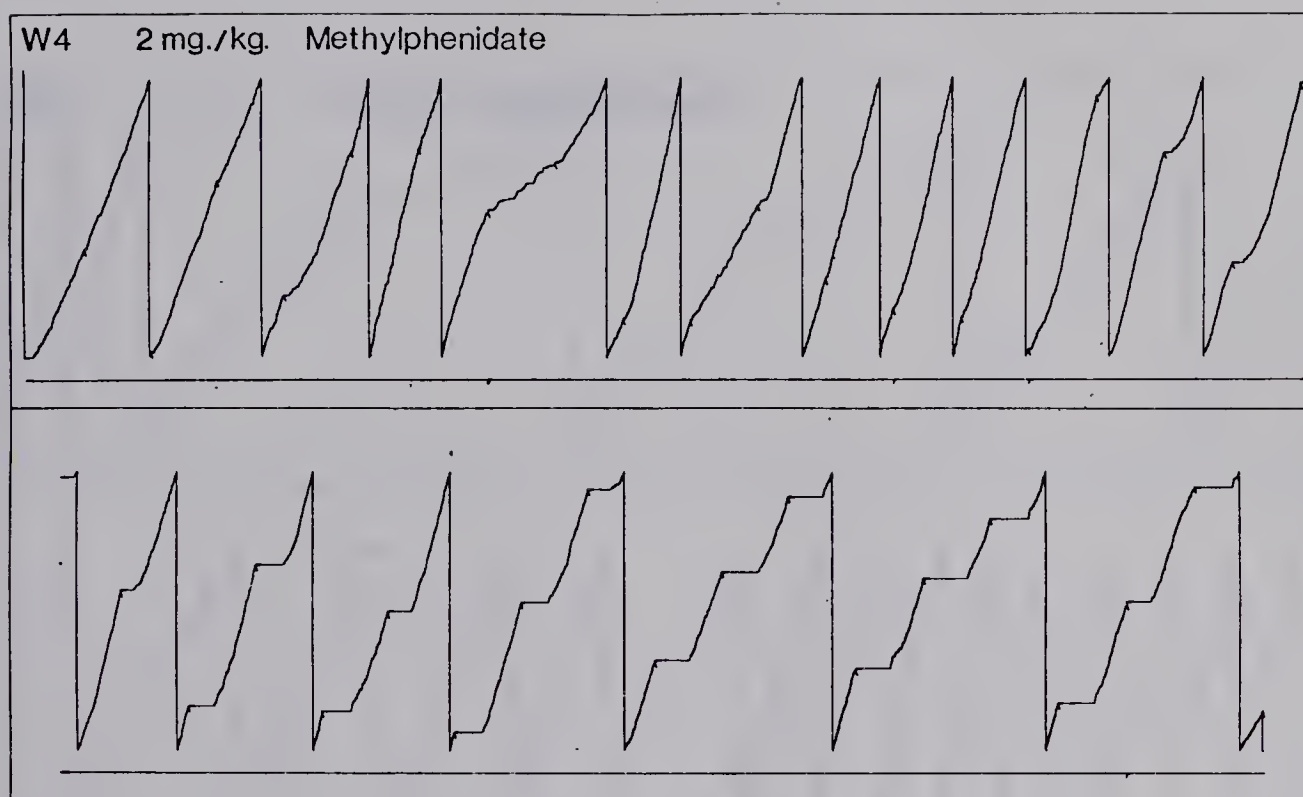


Fig. 20: W_4

Cumulative record of performance on FI 180 LH 2 obtained following administration of 2 mg./Kg. Methylphenidate.

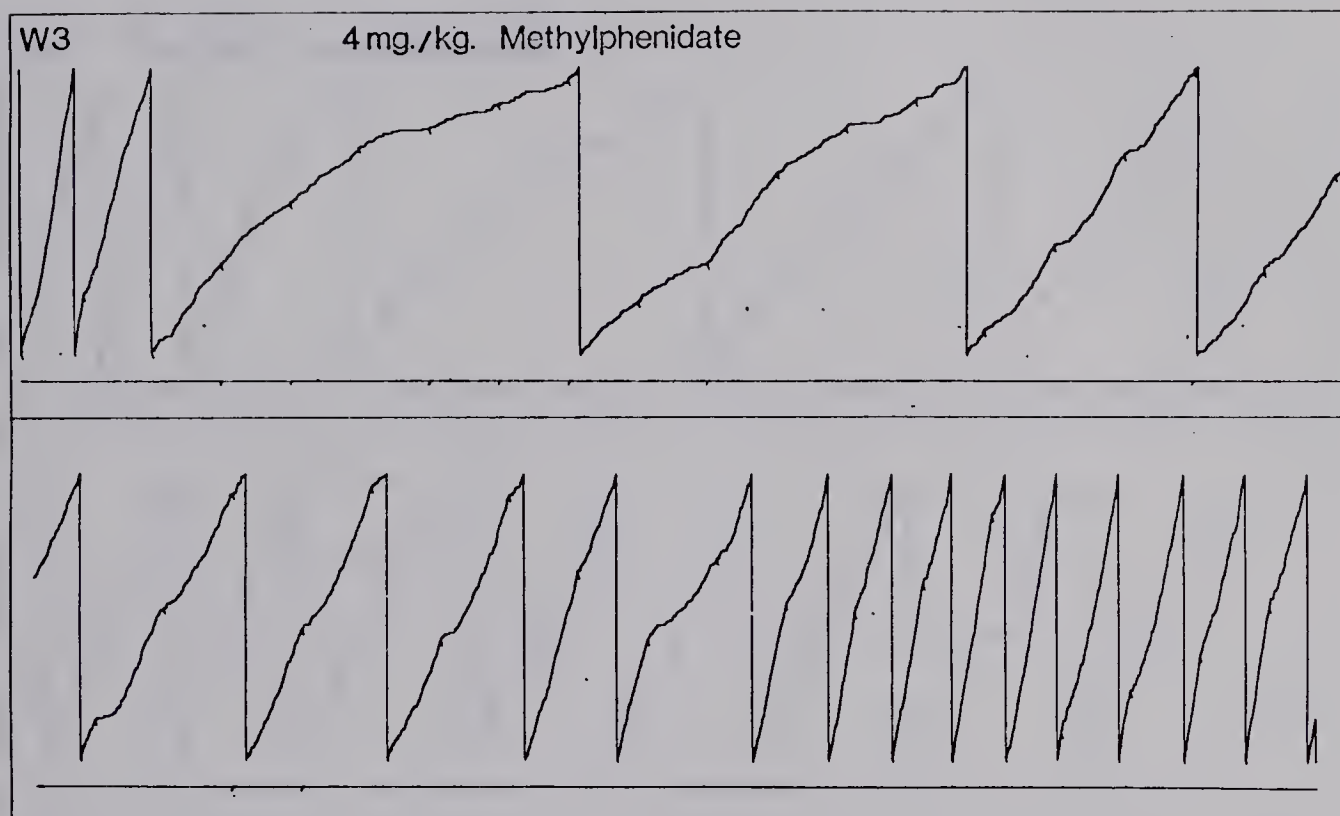


Fig. 21: W₃

Cumulative record of performance on FI 180 LH 2 obtained following administration of 4 mg./Kg. Methylphenidate.

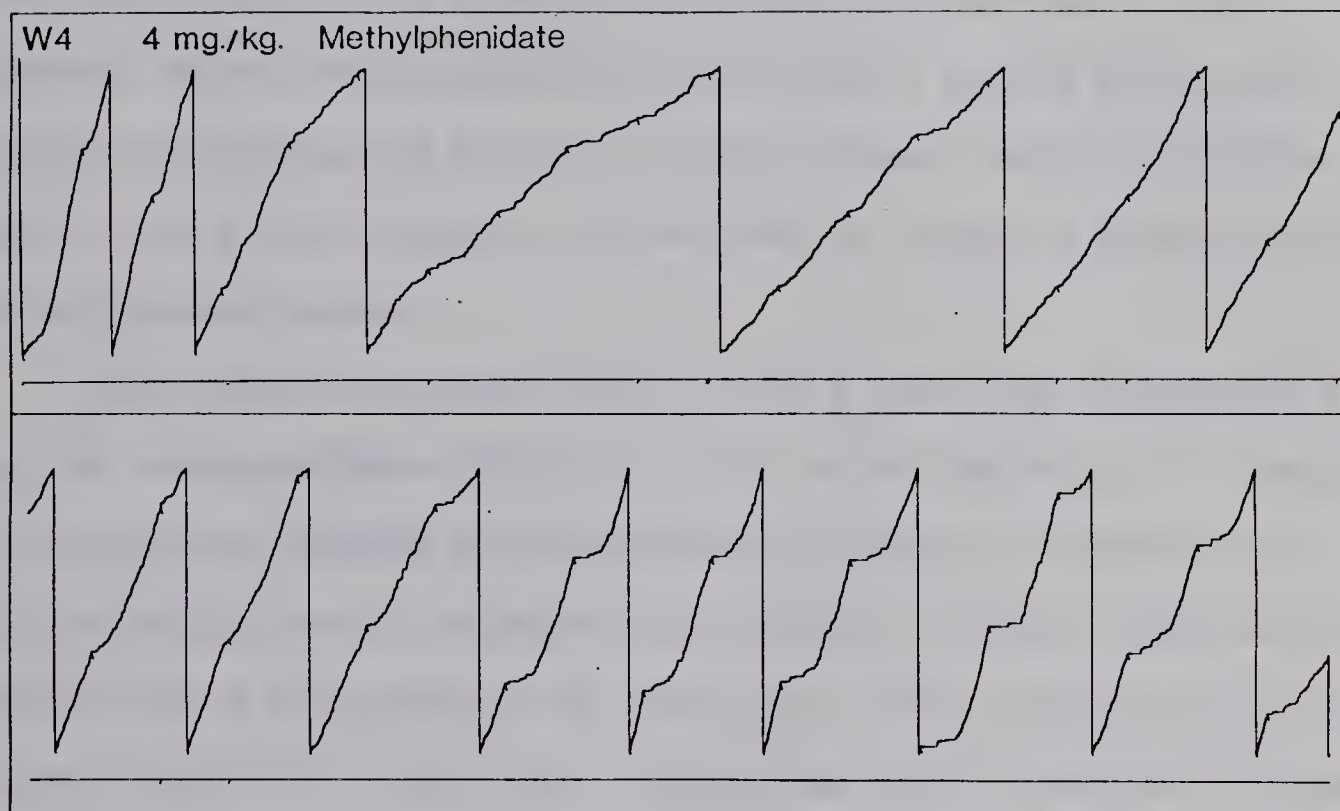


Fig. 22: W₄

Cumulative record of performance on FI 180 LH 2 obtained following administration of 4 mg./Kg. Methylphenidate.

effects were more pronounced. Drug-induced hyperactivity was sufficient to significantly (a) reduce duration of post-reinforcement pausing, and (b) increase response rate, for the entire session. A definite behavioral sequence was observable (Fig. 19): first, a period marked by a moderate increase in response rate and minimal duration of pausing after reinforcement; then a period of high excitation, that is, high behavioral output characterized by continued short pausing plus greatly increased responding; and finally, as drug influence began to diminish, a period during which response rate declined but length of post-reinforcement pausing remained minimal.

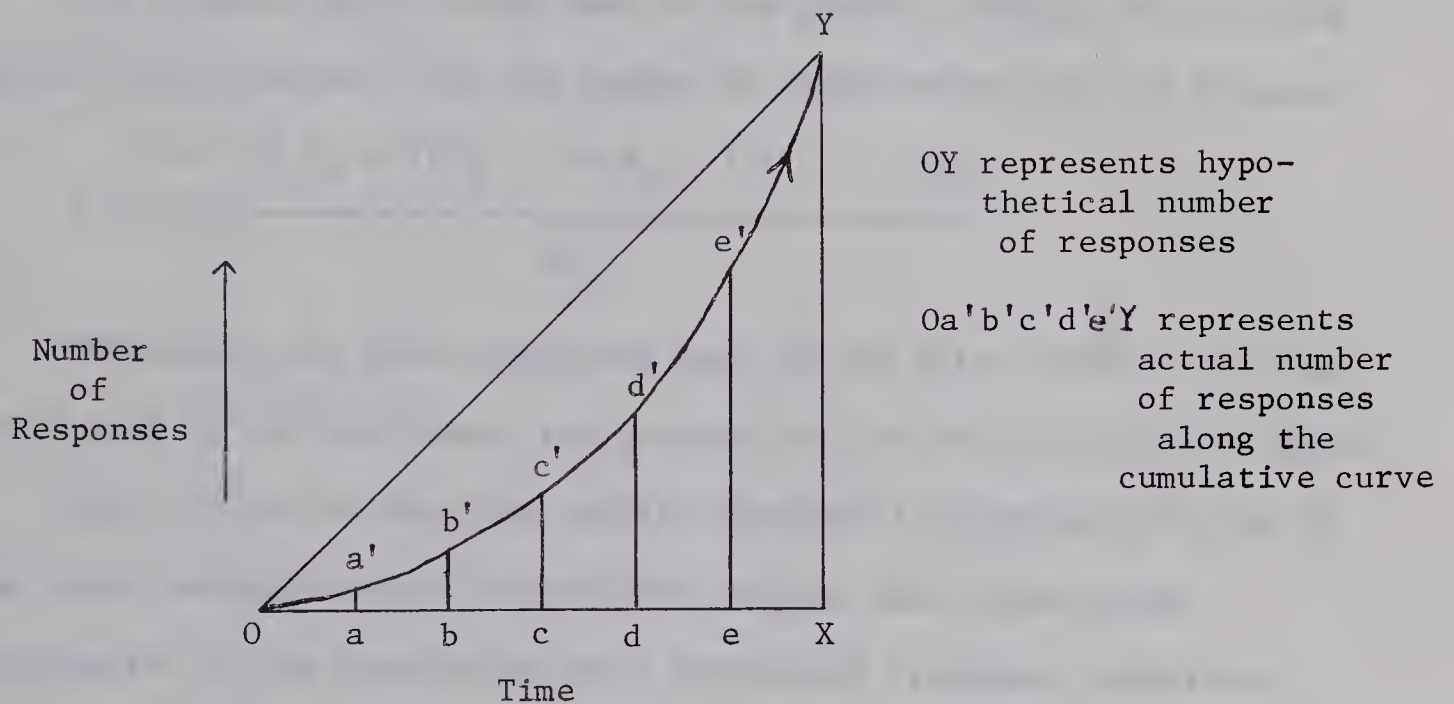
More pronounced effects with W_3 than W_4 were also obtained with 4 mg./Kg. methylphenidate (Figs. 21, 22)². At the beginning of a session, this large dosage reduced post-reinforcement pausing to a minimum and, while increasing overall response rate, depressed the local high end-of-interval rate of responding to the extent that shock frequency rose considerably (Table 2a). In W_3 only, towards the end of a session, this was superceded by the excitatory effect observed previously; with W_4 on the other hand, rather than excitation, a gradual return to control baselines, not completed by the end of the session, followed the initial drug effect.

In evaluation of FI behavior, it was possible to employ a further measure, the mathematical index of curvature (Fry, Kelleher and Cook, 1960), in addition to response rate and duration of post-reinforcement pausing. The major steps of the development will be described here;

²During the first 45 min. period, 4 mg./Kg. methylphenidate induced emesis in W_3 , but only during the first three administrations of the drug.

a detailed account of the derivation is offered in the paper by Fry et al (see References).

Geometric Illustration of Cumulative Record Showing
Assumptions Underlying the Index of Curvature



By calculating the areas of Oaa' , $aa'b'b$ etc., it is possible to obtain the number of responses occurring in each of these segments of the cumulative curve. It can also be shown that aa' equals the number of responses in the first time interval (R_1), bb' the number of responses in the first two time intervals (R_2), cc' the number of responses in the first three time intervals (R_3), dd' the number of responses in the first four time intervals (R_4), ee' the number of responses in the first five time intervals (R_5), and XY the total number of responses (R_6).

Thus, the index of curvature (I) for ∞ FI divided into six subdivisions, as in the present experiment, becomes

$$I = \frac{5R_6 - 2(R_1 + R_2 + R_3 + R_4 + R_5)}{6R_6}$$

i.e., a ratio of actual to hypothetical number of responses.

The formula above is one case of the general formula for dividing the total fixed-interval into any number of subdivisions (n), as follows:

$$I = \frac{(n - 1) R_n - 2(R_{n-1} + R_{n-2} + \dots + R_1)}{nR_n}$$

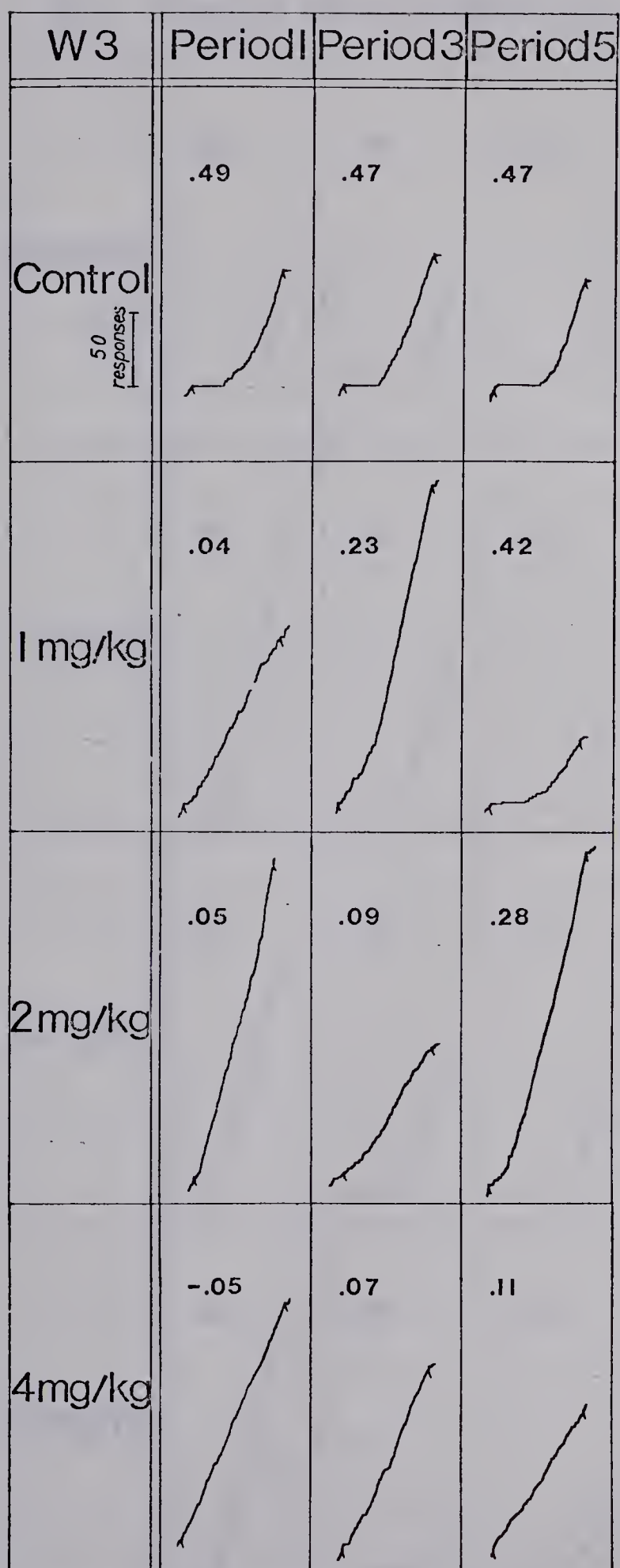
Obviously, the fewer responses made in the first subdivisions and the more made in the last ones, the greater will be the value of the index.

Figs. 23 and 24 show the results obtained from subjects W_3 and W_4 during their methylphenidate Dose-Effect series, each index being representative of the mean index for a particular treatment condition. A number of general findings are readily apparent:

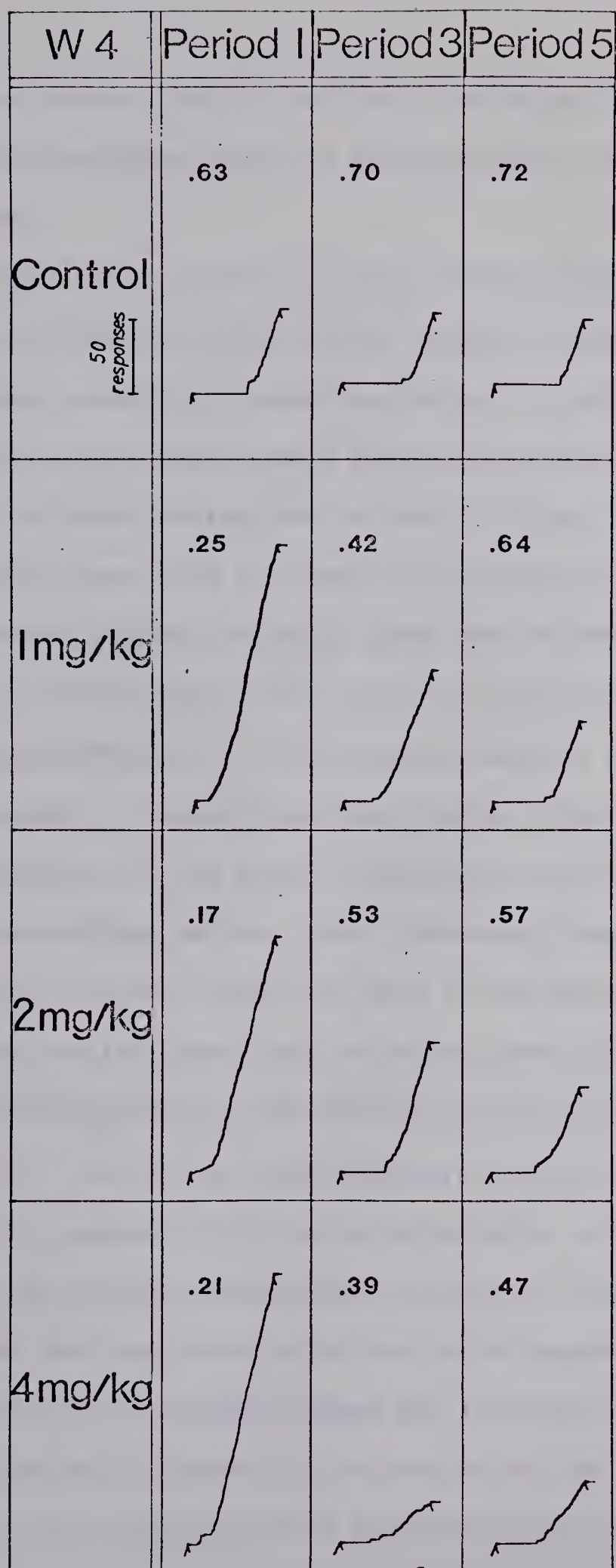
(1) The control values for both animals, none lower than .47, show that there was positive acceleration of response rate over most intervals throughout the experimental sessions.

(2) The control indices for W_4 were consistently higher than those of W_3 but both are indicative of a behavior pattern in which responding is concentrated, in a highly accelerating fashion, towards the end of the interval--in other words, characteristic fixed-interval behavior.

(3) Without exception, the indices values are smaller under drug treatment, demonstrating that methylphenidate invariably affected behavior in the direction of constant responding (a constant rate of responding gives $I = 0$), this effect being greatest near the beginning of the session, and diminishing as the session progressed.

Fig. 23: W_3

Representative indices of curvature for all treatment conditions of the Dose-Effect series for W_3 .

Fig. 24: W_4

Representative indices of curvature for all treatment conditions of the Dose-Effect series for W_4 .

(4) In general, but not entirely, the higher the dosage, the greater was the disrupting effect of methylphenidate on the interval behavior pattern.

(5) Most important, these results indicate that methylphenidate, particularly the 2 mg./Kg. and 4 mg./Kg. dosages, tended to increase rate of response, generating responding during the period that characteristically was the post-reinforcement pause under control conditions. (Confirmation of these findings may be found in Figs. 39c and 40c.)

It was apparent from the cumulative records that at the end of most drug sessions behavior was still under the influence of methylphenidate. Consequently, following the initial series of drug tests a Time Course series was undertaken with W_3 . The results, depicted in Figs. 25 - 28, are self-explanatory. Control baselines (saline injections 90 or 180 minutes pre-session) did not differ significantly from the control baselines of the Dose-Effect series. Overt behavioral changes produced by the drug, though of lesser magnitude, were of the same nature as those observed in the earlier phase, and, as in the case of the ratio animals, appeared to be dependent upon the interaction of dosage level and time since injection. Four mg./kg. methylphenidate injected 180 minutes prior to the start of a session still had an appreciable influence on response rate and duration of post-reinforcement pausing at session completion, indicating that the time course of action of methylphenidate on fixed-interval behavior at the highest dosage was in excess of six hours.

The impression conveyed by the Dose-Effect and Time Course phases of the study is that methylphenidate engendered changes in fixed-interval behavior which were comparable to those induced in fixed-ratio behavior.

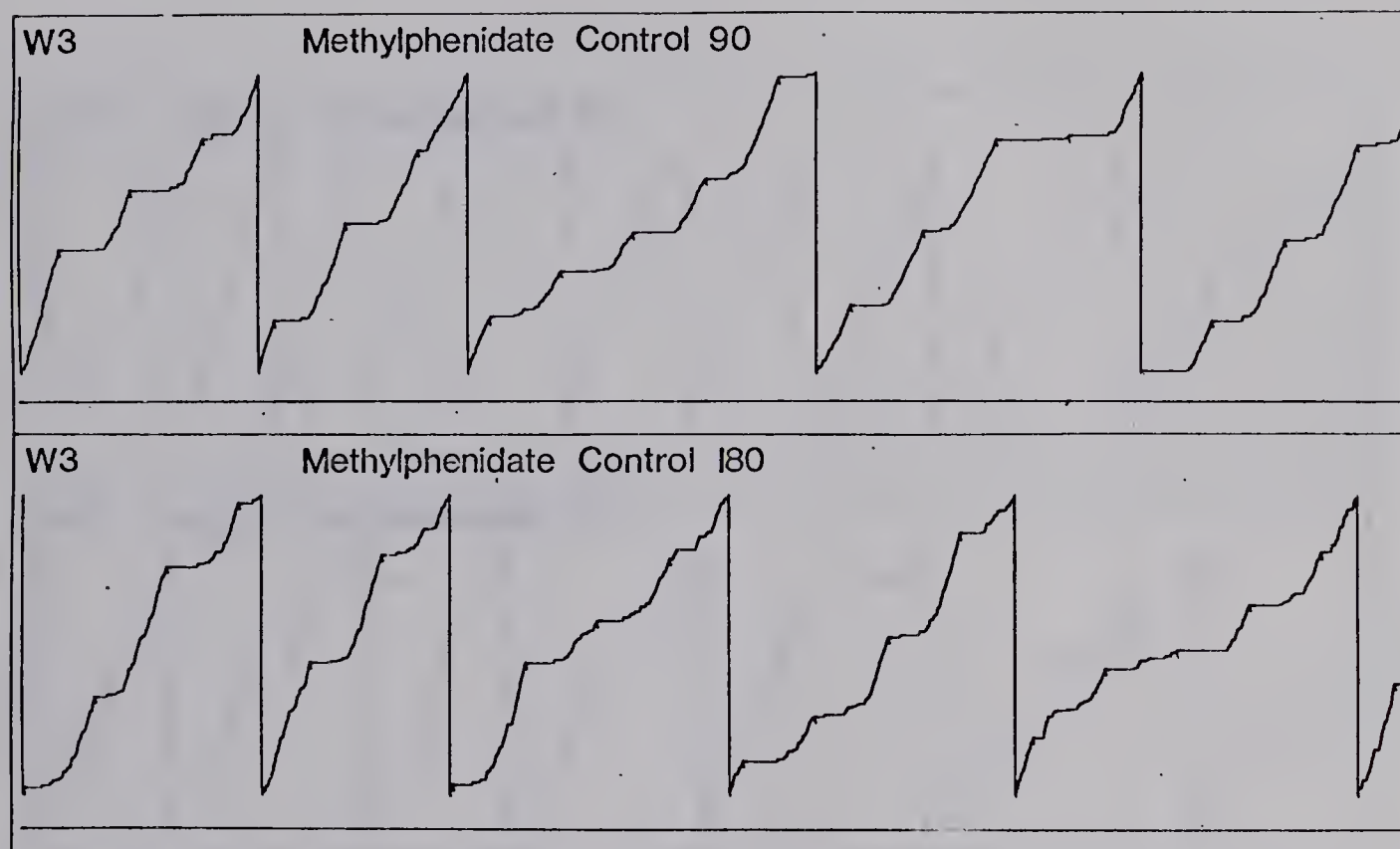


Fig. 25: W_3

Cumulative records of performance on FI 180 LH 2 obtained following pre-session saline administrations.

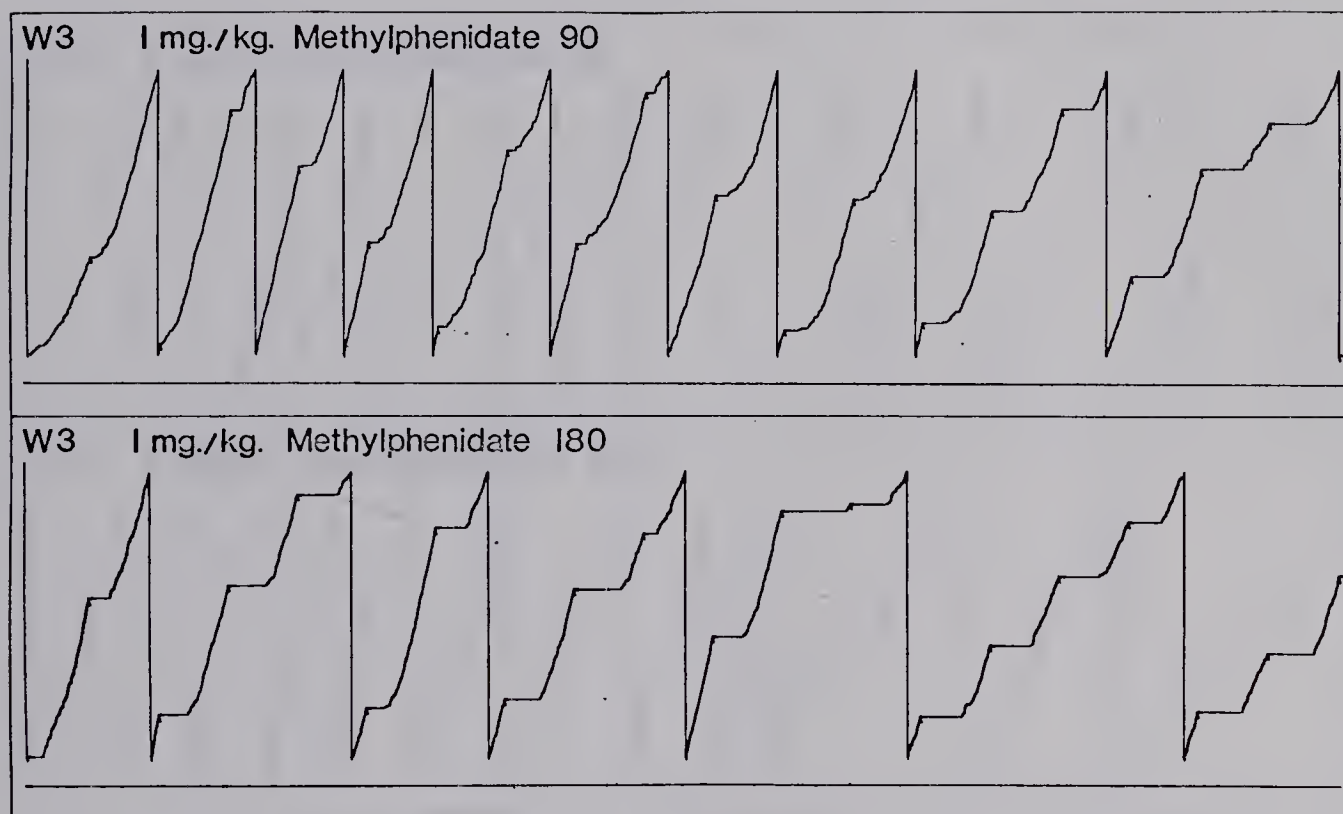


Fig. 26: W₃

Cumulative records of performance on FI 180 LH 2 obtained following pre-session administrations of 1 mg./Kg. Methylphenidate.

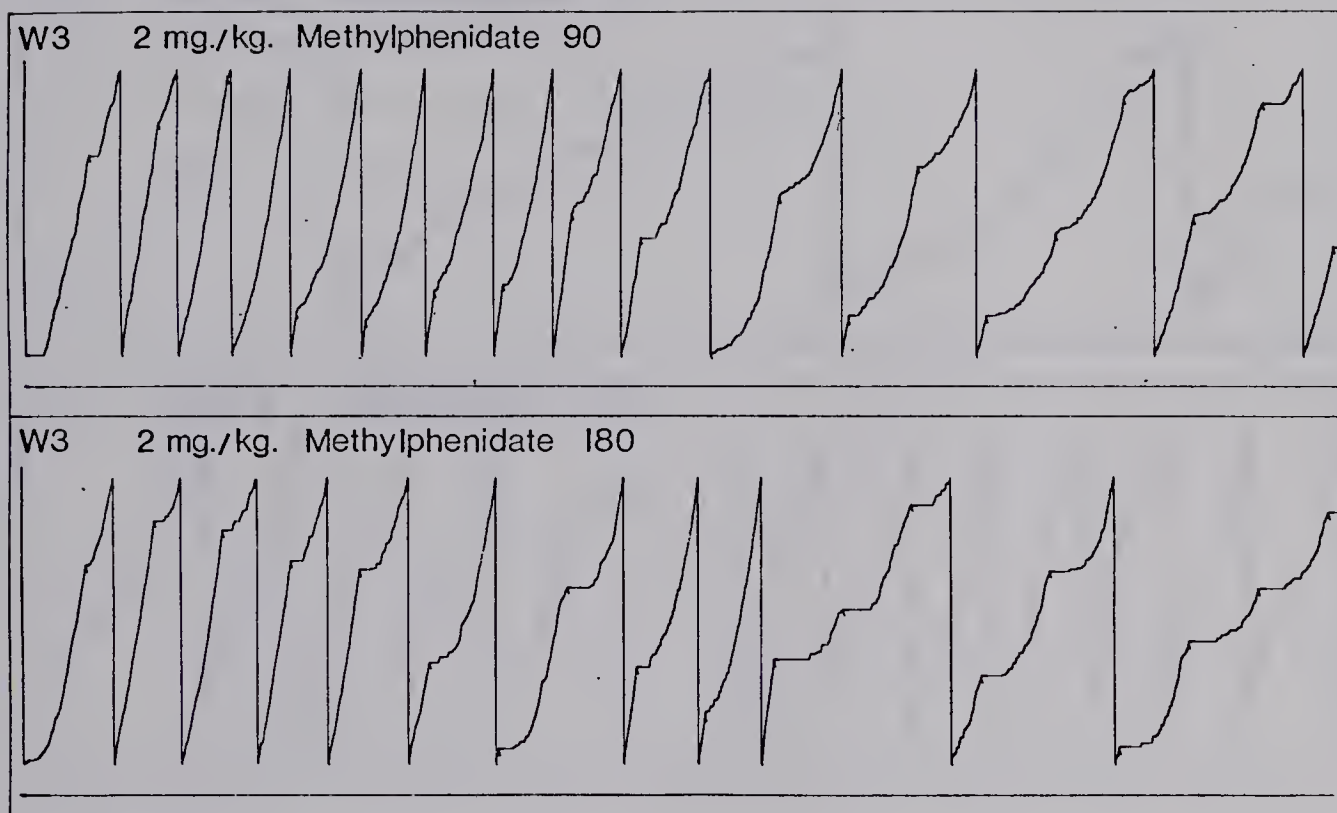


Fig. 27: W₃

Cumulative records of performance on FI 180 LH 2 obtained following pre-session administrations of 2 mg./Kg. Methylphenidate.

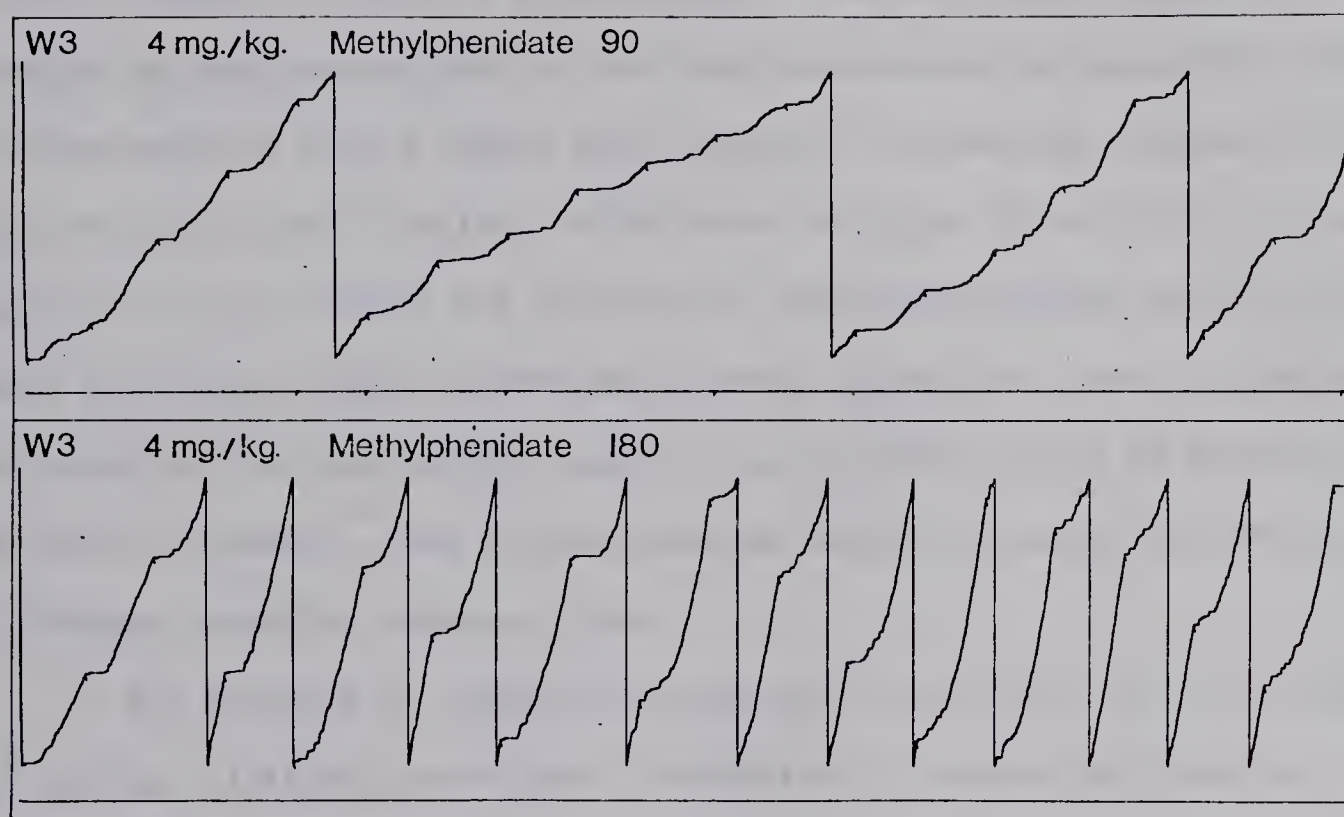


Fig. 28: W_3

Cumulative records of performance on FI 180 LH 2 obtained following pre-session administrations of 4 mg./Kg. Methylphenidate.

As will be made clear in the Discussion, however, this initial impression is misleading, in that it obscures what turns out on closer examination to be a differential effect of methylphenidate on the two behavior patterns.

Finally in this section, the results obtained from W_4 under chronic reserpine treatment are presented. As mentioned in the Method section, W_4 was restabilized at the final parameters following five weeks of convalescence from a broken left forearm. The ensuing behavior differed from the pre-injury baseline, as indicated in Figs. 29 and 41a, b, i.e., response rate was higher and duration of post-reinforcement pausing shorter, these differences being particularly marked during the first 45 minutes of the session. The new control baseline was, however, fully as stable as the initial baseline, and adequate against which to assess the effects of chronic reserpine administration.

The sequence of reserpine dosage levels was 0.05, 0.1, 0.2 and 0.3 mg./Kg. Initially, each level substantially reduced the interval behavior, but after four or five sessions at the first three levels, tolerance developed, and despite the drug behavior began to resemble the control baseline. At this point the dosage level was increased. When, at the 0.3 mg./Kg. dosage level, no tolerance developed, a pronounced reduction in overall response rate was achieved, varying, in terms of the total number of responses per session, from as high as 50% during the first period of a session, and remaining as high as 25% during the final 45 minutes. (Fig. 30). Ten sessions were given under these conditions.

In addition to the reduction in behavior, 0.3 mg./Kg. reserpine invariably produced a curious phenomenon, which can most descriptively be termed "Parkinson-like" convulsions. (Trouton and Eysenck, 1961).

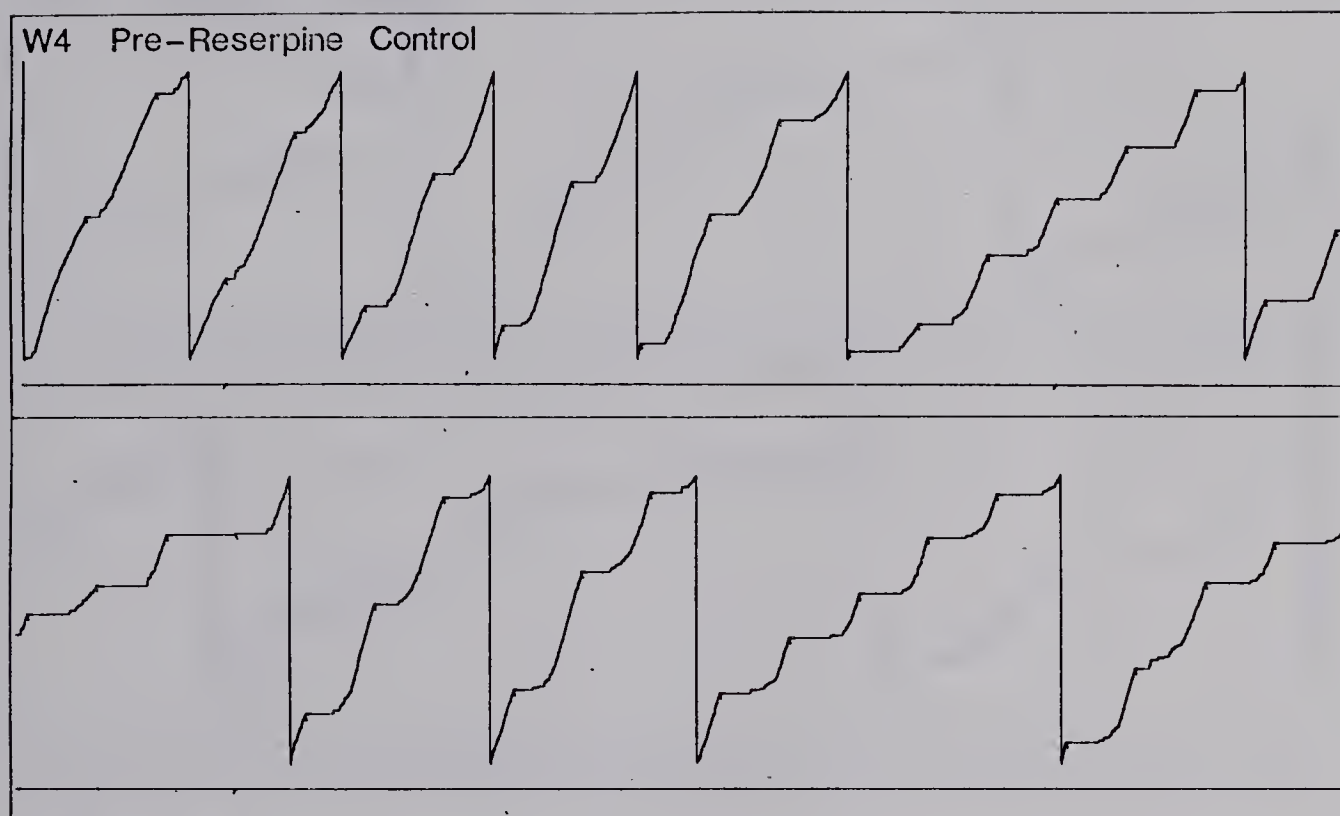


Fig. 29: W_4

Cumulative record of pre-Reserpine control performance on FI 180 LH 2.

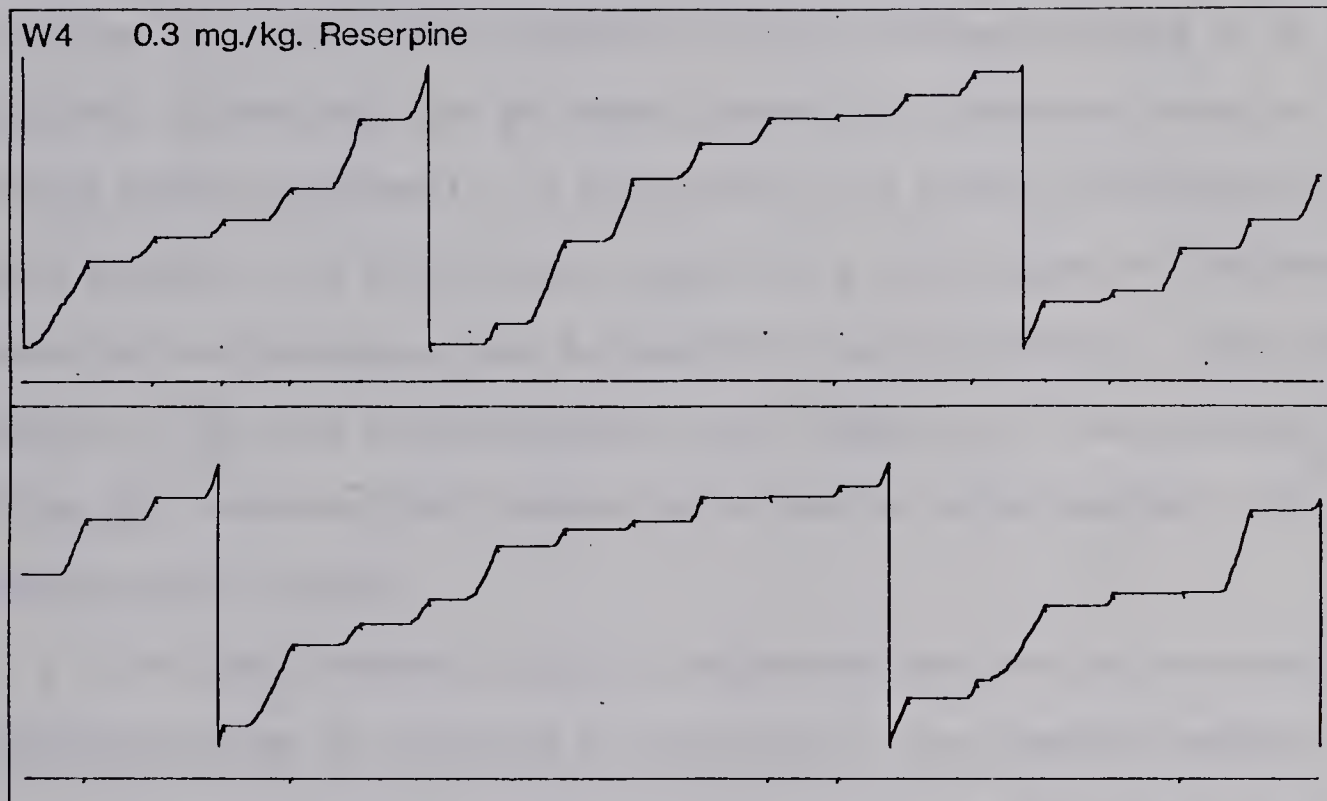


Fig. 30: W_4

Cumulative record of performance on FI 180 LH 2 following administration of 0.3 mg./Kg. Reserpine.

Injection was made immediately following the end of a session, with the animal then being returned to its home cage. Three to four hours later the convulsion syndrome began, passing through the following stages and lasting four to five hours: (1) gradual cessation of spontaneous motor activity, ending in crouching behavior on the perch; (2) prostration on the floor of the cage; (3) periods of ataxic writhing (lasting up to two minutes), alternating with prolonged periods of quiescence (often in bizarre bodily positions); (4) prostration; (5) gradual restoration of motor activity. (A film record, taken over a time course of five hours, describes the phenomenon, and is available from the author.) These side effects of the drug notwithstanding, upon completion of ten sessions at 0.3 mg./Kg. reserpine, the interactive effects of methylphenidate and reserpine were studied.

For five sessions, 2 mg./Kg. methylphenidate was administered immediately prior to the start of the session. The ensuing response rate only superficially resembled that engendered by 2 mg./Kg. alone, consisting of a very substantial initial increase, followed by a gradual decline during the remainder the session (Figs. 31, 41a); also, duration of post-reinforcement pausing (Figs. 31, 41b), although it dropped considerably, was never reduced to the levels characteristic of methylphenidate alone. Obviously, behavior was the product of a reserpine-methylphenidate interaction.

At the completion of this phase, W_4 received five further sessions of 0.3 mg./Kg. reserpine alone, and exhibited fixed-interval behavior very similar to that of the earlier ten sessions at this dosage (Fig. 32). It was interesting to note that the convulsions, which had not occurred

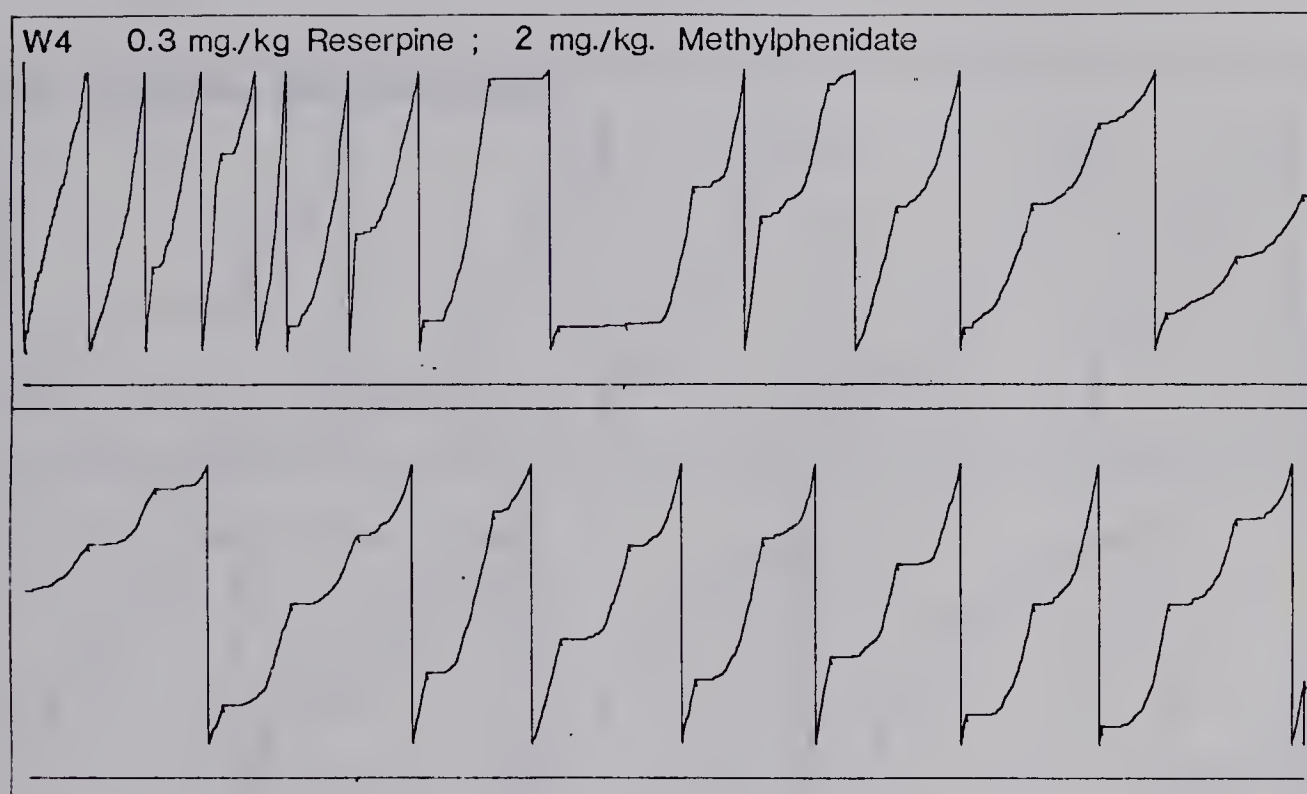


Fig. 31: W_4

Cumulative record of performance on FI 180 LH 2 following administration of 0.3 mg./Kg. Reserpine and 2 mg./Kg. Methylphenidate.

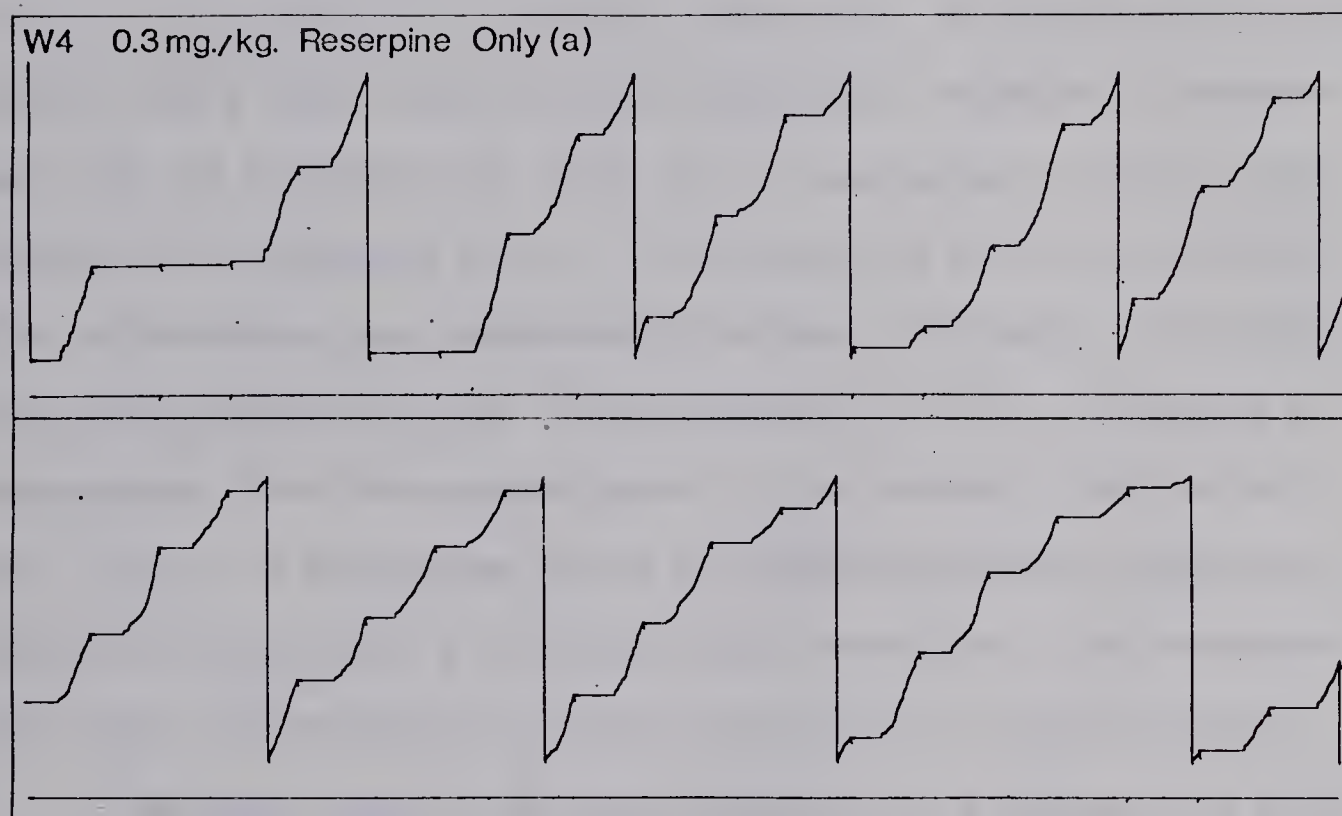


Fig. 32: W₄

Cumulative record of performance on FI 180 LH 2 following administration of 0.3 mg./Kg. Reserpine only (a).

following reserpine-methylphenidate sessions, reappeared following each session with reserpine alone.

The penultimate phase of the study involved combination dosages of 0.3 mg./Kg. reserpine and 4 mg./Kg. methylphenidate. Behavior again resembled only superficially that engendered by the 4 mg./Kg. dosage alone. As with the 0.3 - 2 mg./Kg. combination, the most obvious feature of behavior was a short-lived but very considerable increase in response rate over the reserpine-only level, an increase greater than that produced by methylphenidate alone. In addition, the duration of pausing after reinforcement was substantially reduced, although not as greatly as by methylphenidate alone. Close examination of Fig. 33 reveals a three-phased effect on response rate: (1) an extremely high initial rate, then (2) a mid-session period of *relatively* depressed responding, followed closely by (3) a relatively rapid reversion to the reserpine-only rate. No convulsions occurred following any of these sessions.

The final phase of the study consisted of a further five sessions of 0.3 mg./Kg. reserpine alone (Figs. 34, 41a, b). Although similar to the earlier performances under this treatment condition, behavior was characterized by a response rate that was somewhat higher, and a duration of post-reinforcement pausing ^{that was} somewhat shorter, than previously. This would perhaps indicate that methylphenidate administered daily at a high dosage may reduce the effects of chronic reserpine administration.

Fig. 35 depicts the indices of curvature representative of the reserpinized behavior of W_4 . Two things are immediately apparent: (1) the effect of reserpine only was to further depress the characteristically low rate of responding at the beginning of the interval, resulting, if

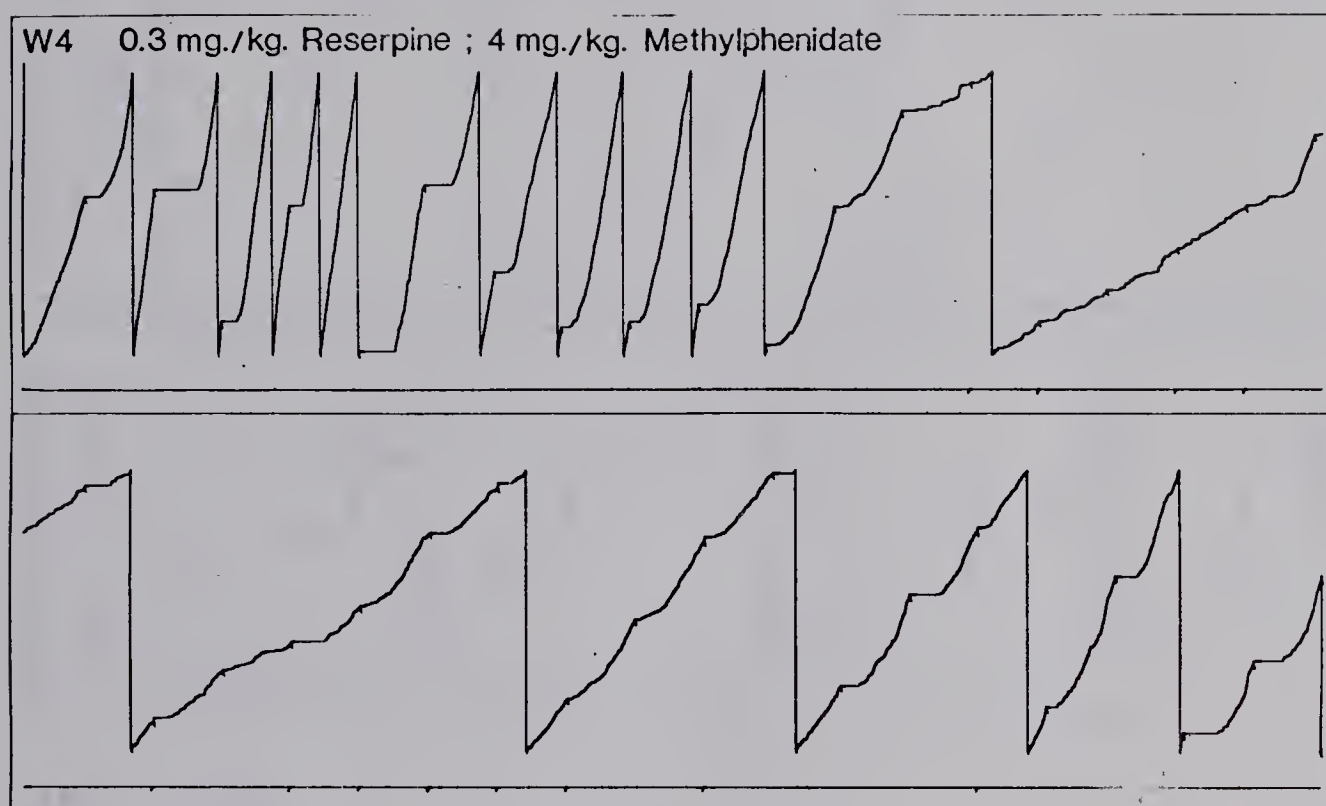


Fig. 33: W₄
Cumulative record of performance on FI 180 LH 2 following administration of 0.3 mg./Kg. Reserpine and 4 mg./Kg. Methylphenidate.

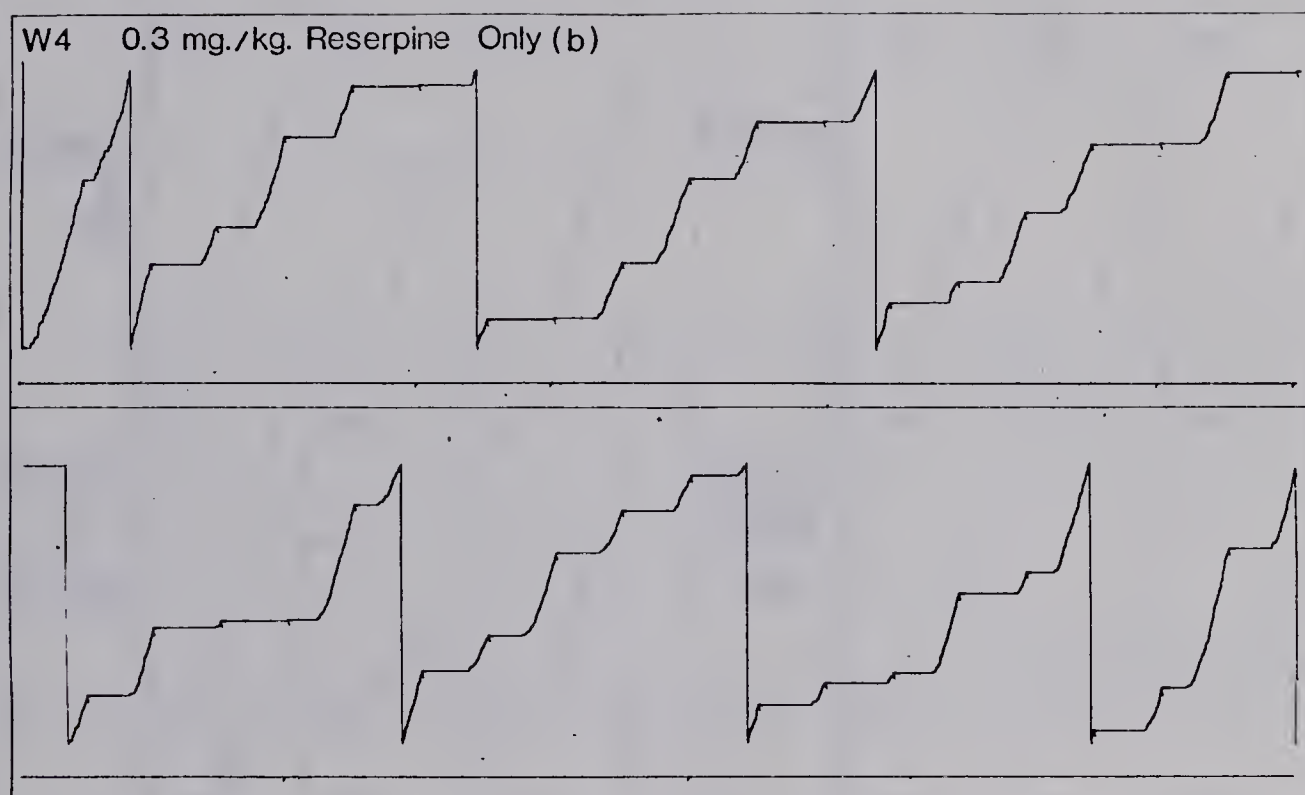
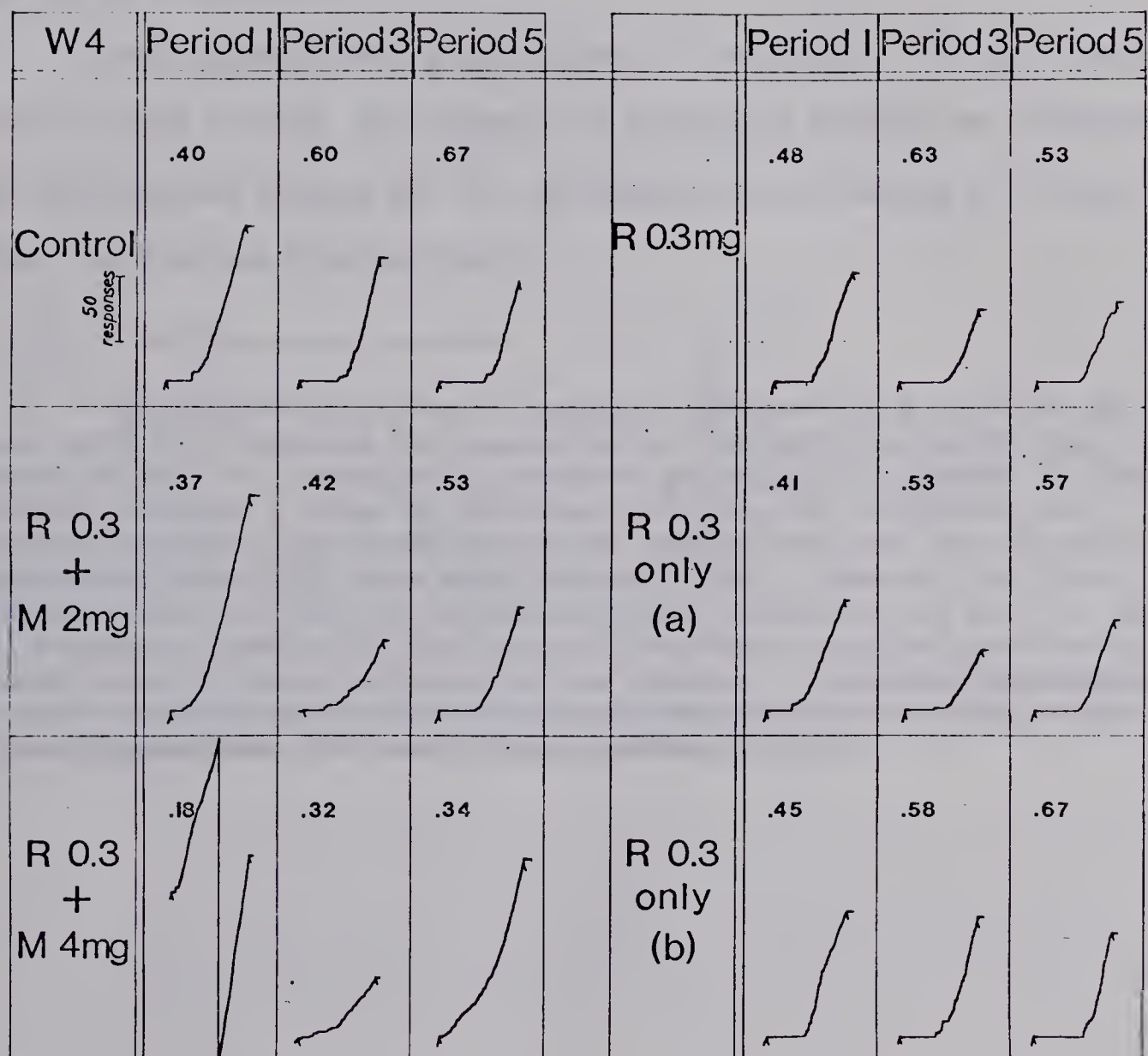


Fig. 34: W₄

Cumulative record of performance on FI 180 LH 2 following administration of 0.3 mg./Kg. Reserpine only (b).

Fig. 35: W_4

Representative indices of curvature for all treatment conditions of the Reserpine-Methylphenidate series of W_4 .

anything, in an overall increase in curvature over control indices; and (2) the effect of methylphenidate was to counteract the rate-decreasing effects of reserpine³.

This concludes the presentation of the results. In the Discussion section which follows, an attempt will be made to explain and interpret the implications arising out of, and tentative conclusions to be drawn from, the findings detailed above.

³It was the intention to replicate the reserpine phase of the study with W₃, following the completion of the methylphenidate Time Course series. W₃ consequently received reserpine at a number of dosage levels, including a final 10 sessions at 0.3 mg./Kg. (Appendix 1c). The characteristic rate-reducing effect and accompanying post-injection convulsions seen in W₄ were also produced in W₃. However, the first administration of 4 mg./Kg. methylphenidate in combination with 0.3 mg./Kg. reserpine resulted in the death of the subject in the conditioning chamber shortly after the start of the session. ~~A possible explanation is that reserpine may have increased the toxicity of the large dosage of methylphenidate, the result being cardiac failure.~~

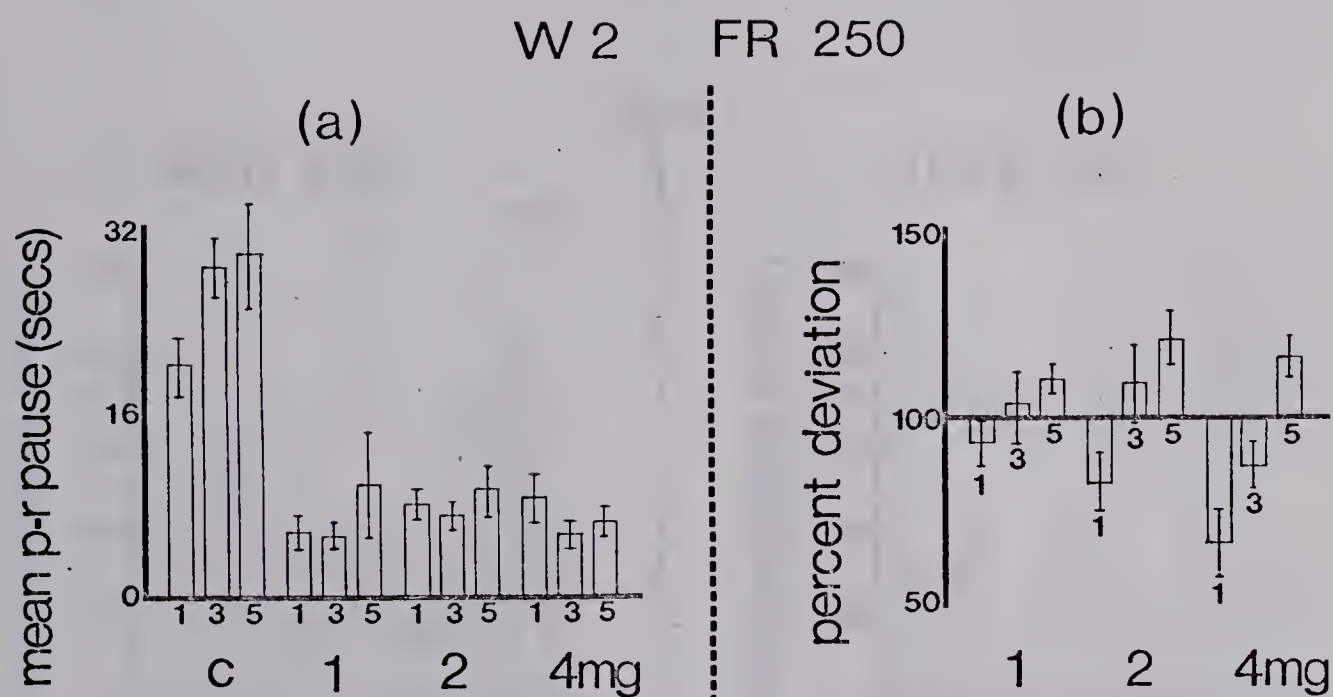


Fig. 36: W₂

Histograms showing: (a) mean duration of post-reinforcement pausing (in seconds) under both control and experimental conditions, and (b) mean response rates per minute under experimental conditions, expressed in terms of percentage deviation from the control values; on FR 250, during the Methylphenidate Dose-Effect series.

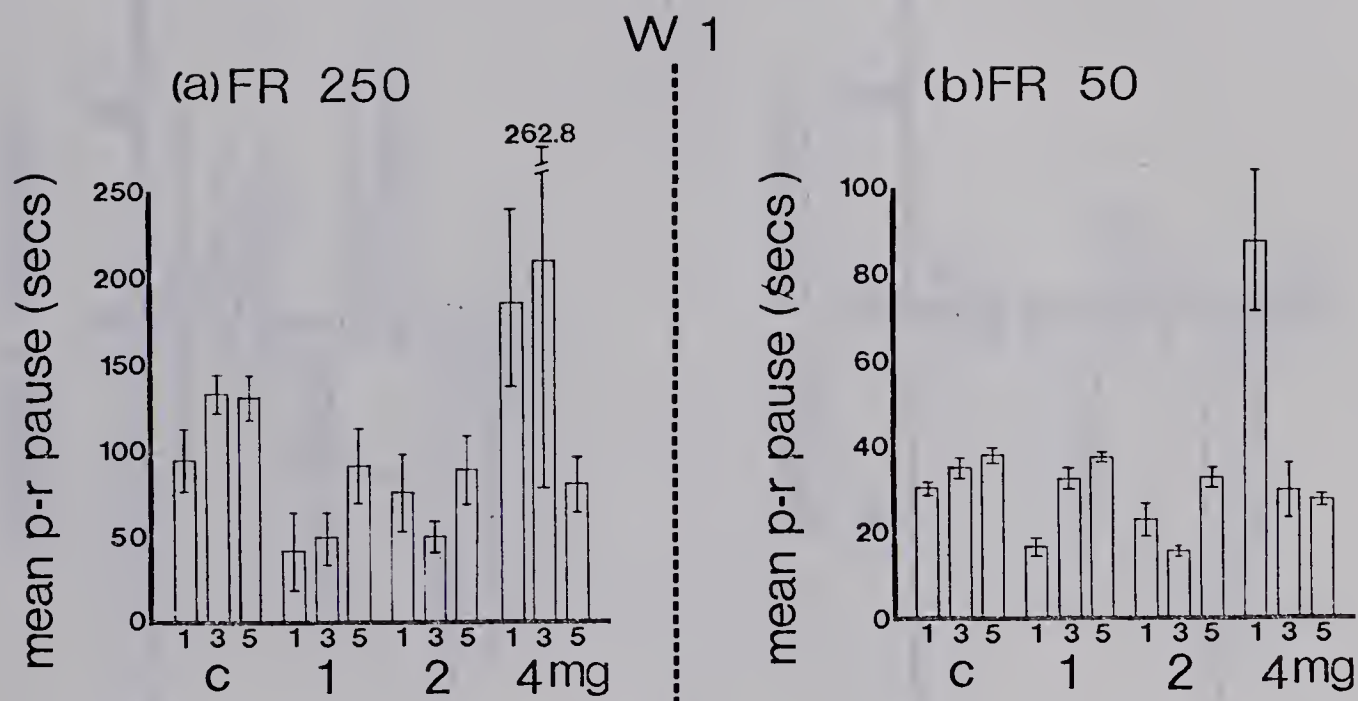


Fig. 37: W_1

Histograms showing mean duration of post-reinforcement pausing (in seconds) under both control and experimental conditions: on (a) FR 250 (b) FR 50, during the Methylphenidate Dose-Effect series.

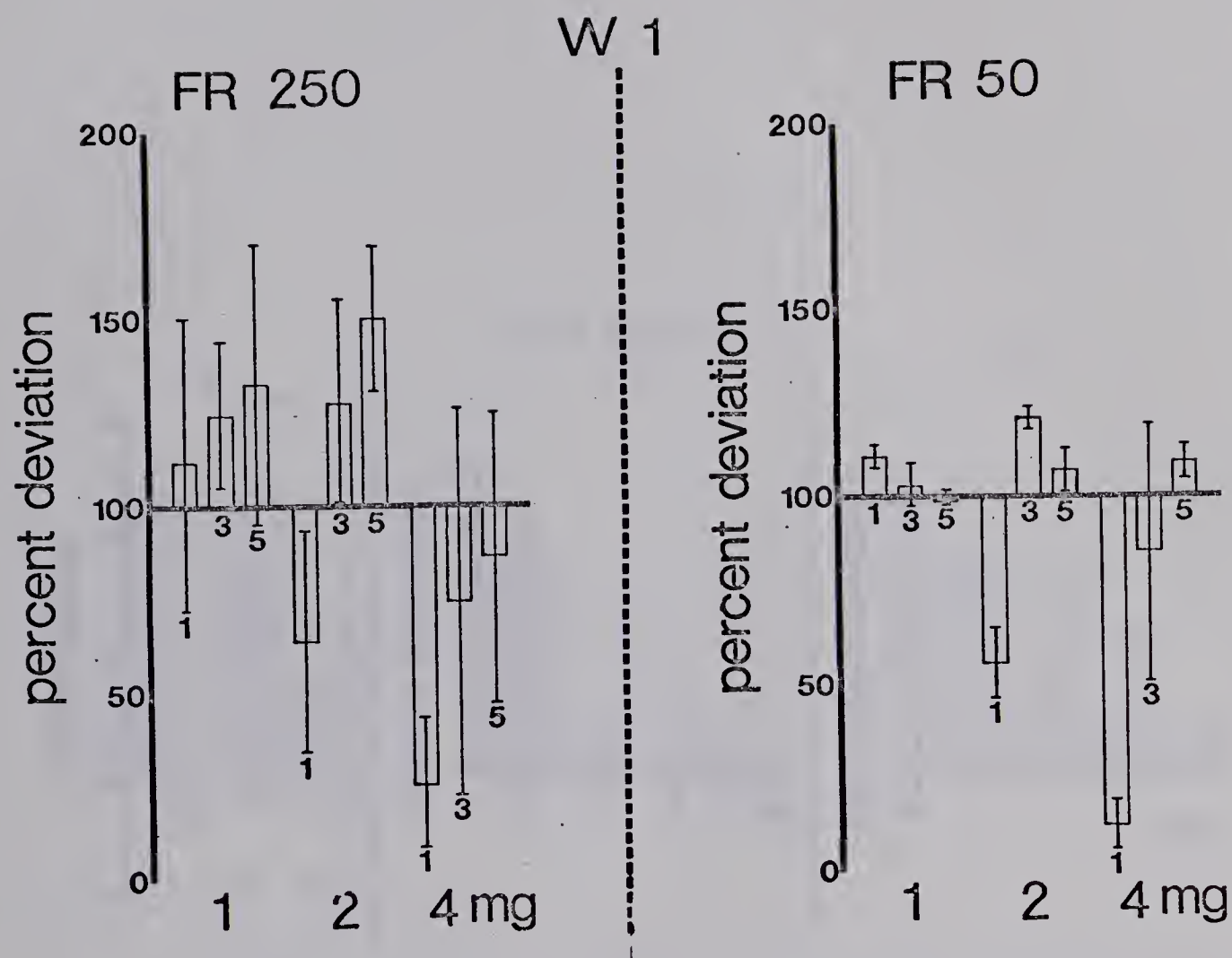


Fig. 38: W_1

Histograms showing mean response rates per minute under experimental conditions, expressed in terms of percentage deviation from the control values: on (a) FR 250 (b) FR 50, during the Methylphenidate Dose-Effect series.

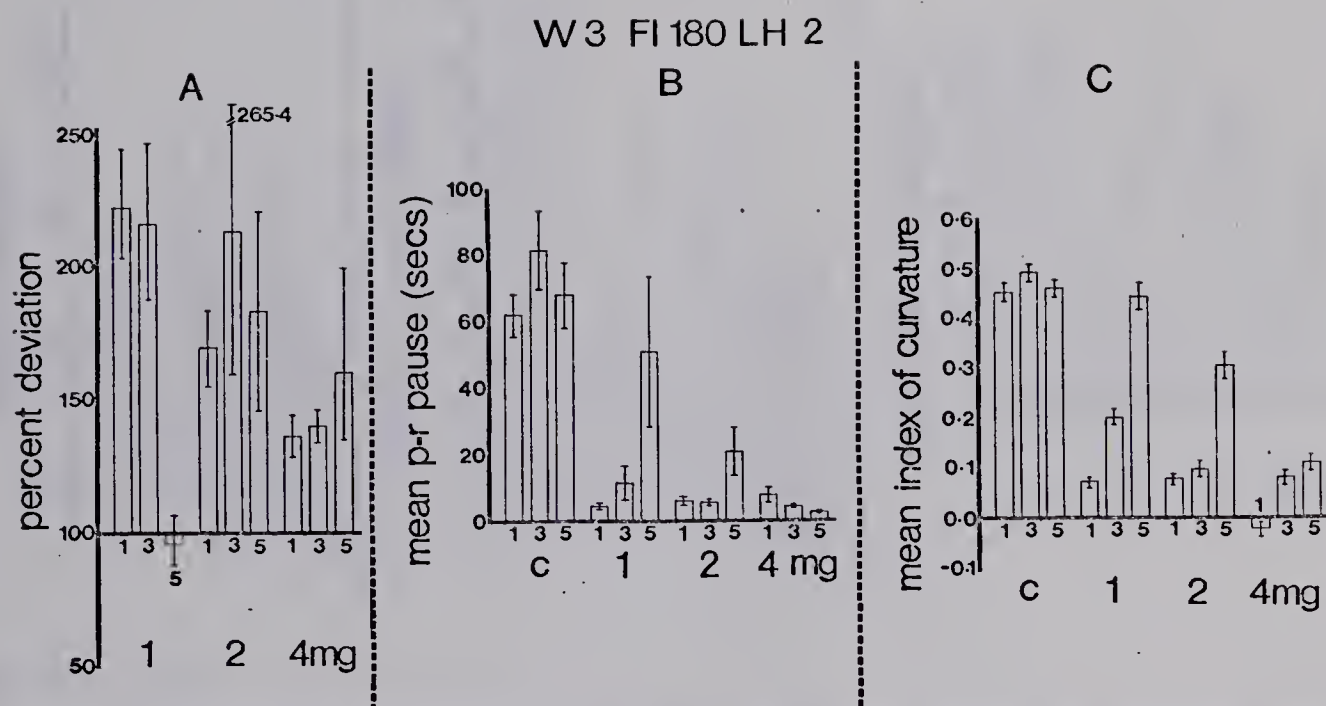


Fig. 39: W₃

Histograms showing: (a) mean response rates per minute under experimental conditions, expressed in terms of percentage deviation from the control values, (b) mean duration of post-reinforcement pausing (in seconds) under both control and experimental conditions, and (c) mean indices of curvature under experimental conditions, expressed in terms of percentage deviation from the control values; on FI 180 LH 2, during the Methylphenidate Dose-Effect series.

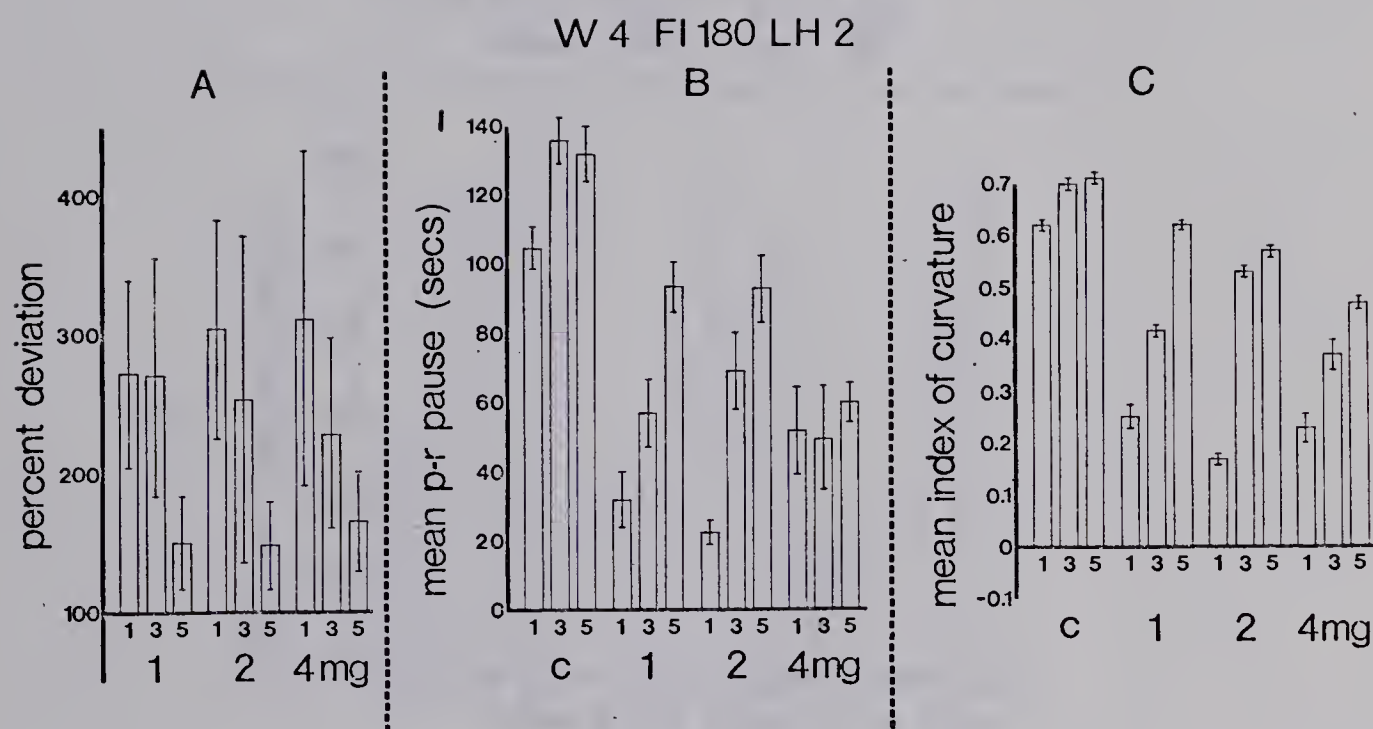
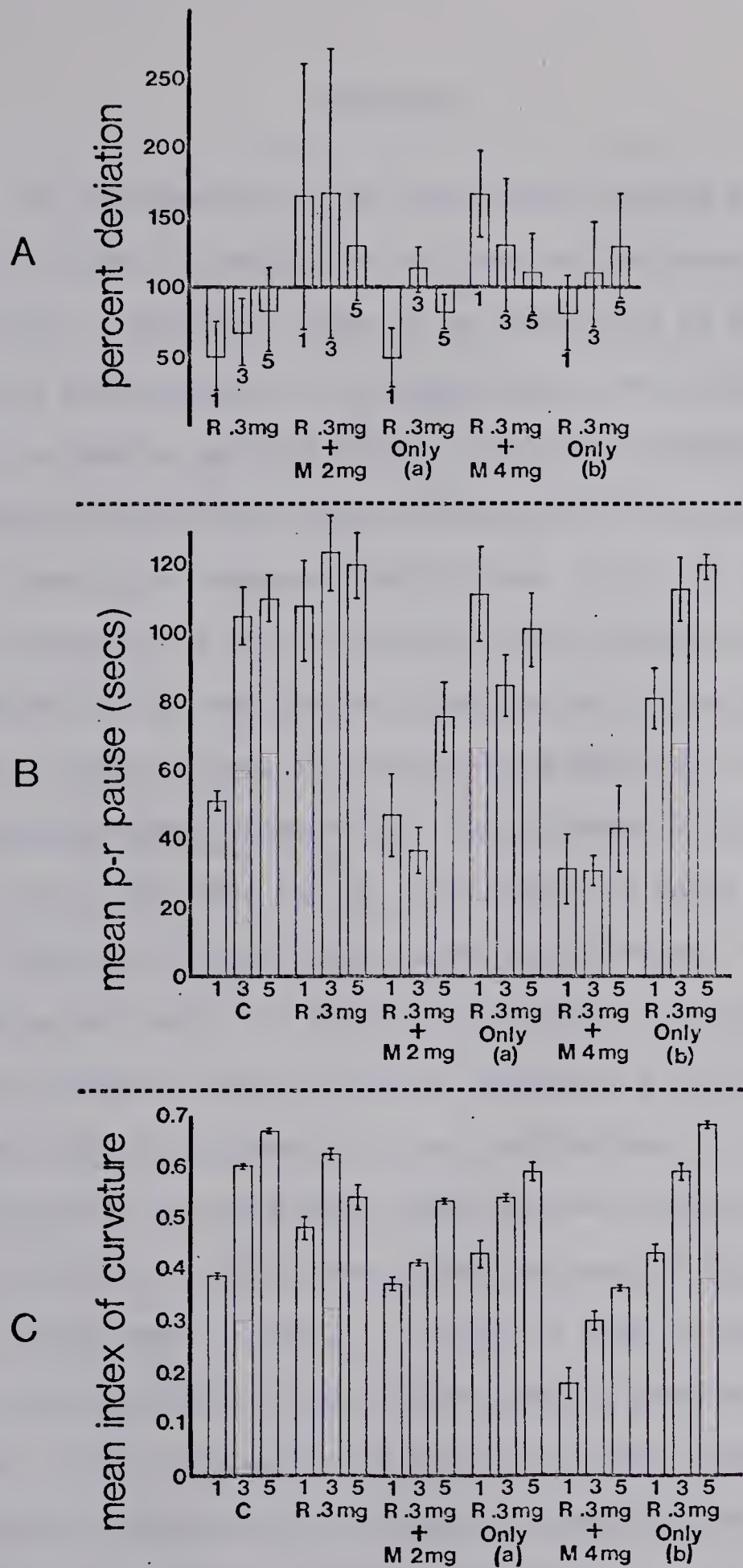


Fig. 40: W_4

Histograms showing: (a) mean response rates per minute under experimental conditions, expressed in terms of percentage deviation from the control values, (b) mean duration of post-reinforcement pausing (in seconds) under both control and experimental conditions, and (c) mean indices of curvature under experimental conditions, expressed in terms of percentage deviation from the control values; on FI 180 LH 2, during the Methyphenidate Dose-Effect series.

Fig. 41: W₄

Histograms showing: (a) mean response rates per minute under experimental conditions, expressed in terms of percentage deviation from the control values, (b) mean duration of post-reinforcement pausing (in seconds) under both control and experimental conditions, and (c) mean indices of curvature under experimental conditions, expressed in terms of percentage deviation from the control values; on FI 180 LH 2, during the Reserpine-Methylphenidate series.

DISCUSSION

The significance of the experimental results can best be demonstrated in terms of the aims of the study as they were outlined in the Introduction. Therefore, prior to an examination of the drug-induced behavioral modifications, it is important to verify first the assumption that the schedules employed induced patterns of behavior characteristic of fixed-ratio and fixed-interval schedules of reinforcement.

Cumulative response records (Figs. 3, 11, 15, 16) show typical control performances for all subjects and illustrate the principal differences in rate and temporal distribution of responding observed under the fixed-interval and fixed-ratio schedules of termination of conditioned aversive stimulation. The FI schedule produced a substantially lower overall rate than the FR, consisting of a pause at the beginning of the interval, followed, once responding had begun, by a steadily increasing rate until the end of the interval; the increasing rate yielded curvature within the record resembling the pattern of responding obtained with an FI schedule of food reinforcement. Compared to FI, FR 250 produced an appreciably higher and more uniform overall rate, which followed an initial pause after the onset of CAS and was continued until reinforcement occurred. In spite of some procedural differences, these data are consistent with those reported previously by Morse and Kelleher (1966) and confirm the view that in most respects, behavior maintained by these schedules resembled closely FI and FR patterns of responding controlled by food reinforcement.

Though primarily directed at behavior-drug interaction effects, the study was also directed at a clarification of the role of reinforcement

in the maintenance of avoidance and/or escape responding engendered by the interval and ratio schedules. Under control conditions, shocks occurred relatively infrequently, for example, W_2 :1.06/hour; W_3 :1.46/hour (Tables 1b, 2a); methylphenidate tended to increase shock frequency in all animals as a function of increasing dosage, for example, at 4 mg./Kg., W_2 received 4.27 shocks/hour, and W_3 received 2.39 shocks/hour. Overall, however, the frequency with which shocks occurred was very low, a fact which permits the following conclusion--that termination of conditioned aversive stimulation, and thus avoidance of shock rather than escape from shock, was the primary source of reinforcement in the present experiment.

Drug-behavior interaction effects constitute the bulk of the findings now to be discussed. The treatment will consider the effects on FI and FR behaviors of, first, methylphenidate, second, reserpine, and lastly, reserpine and methylphenidate in combination.

The overall effects of methylphenidate on the FR and FI behavior patterns engendered in the present study are most readily interpretable within the larger framework of schedule control of behavior. However, one specific effect merits separate mention. Methylphenidate was found to have a temporally differentiable effect on the characteristic segments of both FR and FI behaviors. That is, though the drug markedly affected both duration of post-reinforcement pausing and the patterns of responding leading to reinforcement, the effect was much more long-lasting with the former, a finding which has not been previously reported in the literature.

The general impression conveyed by both observation of the animals in the experimental chamber and inspection of the cumulative records is that methylphenidate induced comparable changes in both FI and FR

behavior: the effect of the 1 mg./Kg. dosage in both cases was to produce, in essence, nothing more than a relatively short-lived increment in behavioral output; on the other hand, 2 and 4 mg./Kg. methylphenidate affected behavioral output in a more complex manner, initially depressing it, then stimulating it to well above the control levels to which it gradually reverted several hours after drug administration, the rapidity of reversion varying inversely with dosage level.¹ These effects seemed to be more pronounced in the interval animals.

This initial impression, though correct, is not the only or the best interpretation possible. A more penetrating alternative explanation emerges on closer examination of the data. Figs. 36b and 39a demonstrate that methylphenidate affected FR and FI response rates differentially. Rate-decreasing effects of the drug were observed during the first 45 minutes after injection as an increasing function of dosage when responding was maintained by FR 250, but such rate changes were less pronounced relative to the changes produced when the drug was administered to W_3 and W_4 . Methylphenidate produced substantial rate increases under the FI schedule, although the effect during the first 45 minutes after injection was inversely related, and during the last 45 minutes of the session positively related, to dosage.

¹Throughout the Time Course series for both W_2 and W_3 , the animals were returned to the home cage after injection to await the start of the session. During this time there was no control over their activity. Consequently, beyond noting that, in general, methylphenidate at dosage levels of 1, 2 and 4 mg./Kg. caused both ratio and interval behaviors to differ significantly from control levels for several hours (in excess of six hours at the highest dosage), the data from this phase of the study were treated with caution.

A number of figures show the effects of methylphenidate for two further performance measures. First, the drug consistently reduced the pause immediately following the onset of CAS as compared with the control performances of W_1 and W_2 (Figs. 37b, 36a). Second, calculation of the average index of curvature for FI behavior (W_3 and W_4) showed that methylphenidate modified the temporal patterning of responses characteristic of FI control performance (Figs. 23, 24). Confirmation of these trends may be found in several other figures.

This differential effect of a psychomotor stimulant is readily interpretable in the light of the suggestion by Dews (1958a) that the effects on operant behavior of the amphetamines are determined largely by how frequently the response being studied occurs. If the control response rate is low, these drugs will increase the rate (Sidman, 1956; Morse and Herrnstein, 1956; Schuster and Zimmerman, 1961; Kelleher, Fry, Deegan and Cook, 1961; Zimmerman and Schuster, 1962; Smith, 1964). By contrast, if behavior under control conditions occurs relatively frequently (Dews, 1958b; Owen, 1960; Kelleher et al, 1961; Smith, 1964) the amphetamines will decrease the overall rate of responding. The present results appear to confirm and extend Dews' hypothesis, since methylphenidate, a psychomotor stimulant with similar effects to amphetamine, (a) increased the relatively low response rates and abolished the positively accelerated pattern of responding characteristic of FI non-drug control performance, the latter effect being largely the results of increased responding during the early part of the interval, (the post-reinforcement pause), and (b) although exerting a less pronounced effect on overall FR

response rate, consistently reduced the period characterized under control conditions by an absence of lever pressing occurring immediately after the onset of CAS (the post-reinforcement pause), and at the same time diminished the high terminal rate once responding had begun, these effects being most pronounced at a dosage of 4 mg./Kg.

Before concluding the discussion of the effects of the psychomotor stimulant, methylphenidate, an important point must be made, which will show the Dewsonian interpretation of the present results to be part of the larger framework of the role of the schedule of reinforcement in the control of behavior. "Psychomotor stimulant" implies that a drug to which the term is applied invariably causes an increment in motor activity when administered to an organism. In recent years, behavioral pharmacologists have shown that this is not inevitably the case (as the complex sequence of rate-increasing and rate-decreasing effects induced by methylphenidate within the same session adequately demonstrates in the present study), and have further established that the behavioral effects of both psychomotor stimulant and depressant drugs are influenced considerably by the nature of the situation in which the subjects are placed. Morse (1962) discussed this whole issue in detail:

In recent years, dramatic demonstrations of differential sensitivity to a drug in different situations have helped to establish the importance of environmental variables in determining the behavioral effects of drugs. But, since the selective modification of behavior by drugs is the rule rather than the exception, the problem for behavioral pharmacology today is to go beyond the mere demonstration of differences. It must systematize and clarify the nature of the interactions between the effects of drugs and environmental determinants of behavior. A first step is to isolate and specify more exactly which environmental variables are most important in influencing the action of a drug on behavior.

The Review of the Literature clearly pointed out that some of the best demonstrations of this dependence of drug effects on environmental factors were found in studies which employed operant techniques, where the environment was rigidly controlled. For example, as early as the mid 1950's, Dews (1955a) had shown that the effects of sodium pentobarbital on a learned response in pigeons depended on the schedule of reinforcement used to maintain the response.

Kelleher and Morse (1966) recently extended Dews' suggestion. Taking the lead from Dinsmoor (1962), who reported an experiment in which behavior was maintained by termination of stimuli associated with aperiodic delivery of noxious stimulation, and Azrin et al (1962), Kelleher and Morse demonstrated the maintenance of patterns of responding characteristic of FR and FI schedules of food reinforcement but in which response rates were reinforced by termination of a "schedule complex" consisting of exteroceptive stimuli associated with brief electric shocks. The authors therefore proposed that the schedule of reinforcement may be more important than the nature of the reinforcer in the control of operant behavior.

In the light of two findings of the present experiment, which were pointed out earlier and are reiterated here, further validity is imparted to this suggestion of Kelleher and Morse: (1) The interval and ratio behavior patterns generated were identical in every respect to behaviors maintained by comparable schedules of positive reinforcement; and (2) Termination of conditioned aversive stimulation constituted the primary source of reinforcement.

Considered together, these observations give support to the statement by Kelleher and Morse that

. . . different kinds of events such as presentation of food and termination of electric shocks are alike only in that they are both reinforcers.

Their contention is thus that it is the schedule rather than the nature of reinforcement which is important in the maintenance and control of behavior--more specifically, that comparable schedules produce comparable drug-behavior dependencies when responding is maintained either by positive or by negative reinforcers.

A further demonstration of the importance of the schedule to the maintenance of behavioral control emerged from the ratio performance of W_1 . The original schedule, it will be recalled, imposed behavioral strain on the animal, such that the training period was frequently interrupted by disruptions of behavior, and performance once the final parameters had been reached was characterized by instability. In effect, the ratio behavior was under weak schedule control. However, when the parameters were reduced, schedule control developed satisfactorily, with the result that behavior at FR 50 was stable and predictable under both control and drug conditions.

Blough (1958) demonstrated a similar phenomenon. Briefly, a hungry pigeon stands in a darkened chamber and views a variable patch of light. Continued pecking on key A reduces the intensity of the light, so that eventually it is no longer visible, at which point a peck on key B causes delivery of a food reinforcement and a simultaneous increase in the intensity of the stimulus, so that it becomes visible

again. When this happens the bird again switches to key A, and thus over a period of time plots a graph representing its own visual threshold.

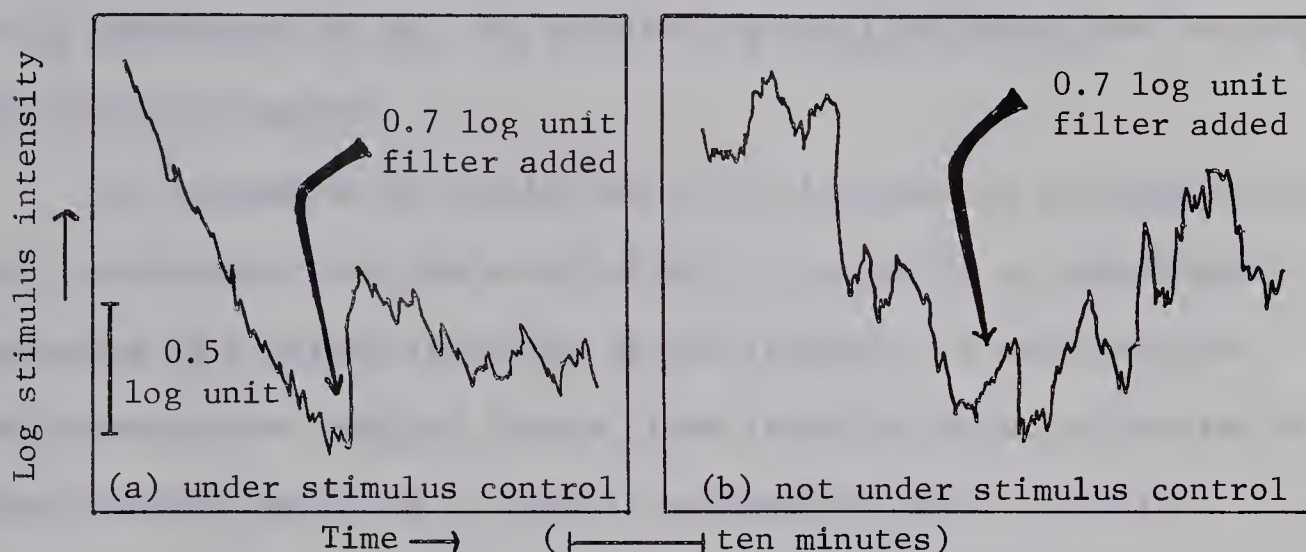


Fig. 42: Result of a test for stimulus control. The falling curve results from dark adaptation. (Adapted from Blough, 1958).

Fig. 42 illustrates the importance of schedule control to this behavior. The graph on the left represents the performance of a bird under schedule control and, as Stretch (1966) points out, the record reveals an extremely important point--the bird compensates rapidly for a decrease in the intensity of the stimulus when a filter is added. However, if the degree of behavioral control attained by the reinforcement contingency is not satisfactory, performance remains erratic and highly variable, and a change in stimulus intensity produces no easily discernible effect (graph b).

Both the study by Blough (1958) and the results obtained from W_1 in the present experiment demonstrate the importance of schedule control of behavior. That is, if a behavioral baseline is to be a reliable measure of drug effect, for example, then the schedule employed must exert reliable control over that baseline.

This concludes the treatment of the effects of methylphenidate. Considering now the effects of chronic administration of reserpine on the FI performance of W_4 , the results are straightforward and require only brief discussion.

As documented in the Review of the Literature, previous studies have demonstrated that the major effect of reserpine on conditioned responding is a marked reduction in the frequency of occurrence of that response over control levels, such reduction being a function of a drug-induced reduction in overall spontaneous motor activity.

In the present study, behavioral changes from the control baseline induced by the test dosage level of reserpine (0.3 mg./Kg.) are readily apparent in a comparison of Figs. 29, 30 and 35. The major effect was a doubling of the duration of post-reinforcement pausing--in effect, a prolongation of the low (zero) rate of responding characteristic of the first part of an inter-reinforcement interval. With respect to the end of the interval, though the drug reduced the number of responses made, indices of curvature under reserpine were similar to control indices. Taken in combination with the increased length of pausing after reinforcement, this could only be the case if response rate was higher, relatively, than under control conditions. In other words, reserpine increased the high control rate of responding that was characteristic of the latter part of the interval. It is thus apparent that reserpine had the opposite influence on FI behavior to that of methylphenidate, acting in a manner contrary to that proposed for psychomotor stimulants by Dews (1958a); however, reserpine being a psychomotor depressant, this finding was not unexpected.

The convulsions produced by daily administration of 0.3 mg./Kg. reserpine, and the rapid development of tolerance to smaller dosages (as outlined in the Results section), were additional effects of reserpine on the behavior of W_4 .

In summary of this portion of the Discussion, the present study indicates a number of things: (1) that reserpine has opposite behavioral effects on the FI behavior of the squirrel monkey to those of methylphenidate, that is, reserpine decreases low rates of responding and increases high rates of responding (a further demonstration of the important role of the schedule of reinforcement in the explanation of a drug-behavior interaction); (2) that there exists a dosage level of reserpine, probably peculiar to the individual subject, which reduces behavioral output without leading to the development of tolerance; and (3) that daily chronic administration of this same dosage level of reserpine induces protracted Parkinson-like convulsions commencing about four hours after injection (a phenomenon observed previously by Davis (1957), Weiskrantz (1958) and Trouton and Eysenck (1961)), symptomatic of a drug-accumulation effect.

The consensus of opinion in the studies cited in the Review of the Literature concerning reserpine-methylphenidate interaction was that the effects of combination were not those of mutual neutralization, but rather were the exhibition of the effects of methylphenidate alone, to the apparent exclusion of reserpine effects. However, this was not the case in the present study.

After chronic reserpine pretreatment, methylphenidate was administered in two dosage series--2 mg./Kg. and 4 mg./Kg. In both cases the drug restored responding (the degree of restoration being

proportional to the dosage level), and cumulative records resembled those obtained from comparable sessions with methylphenidate alone. It was immediately apparent, however (Figs. 31, 33), that the resemblance was superficial: (a) at the time of maximal action of methylphenidate, i.e., the first 45 minute period, the reserpinized animal emitted behavior at a rate that was far in excess of the rate seen in sessions with methylphenidate alone (Figs. 20, 22), this effect being largely the result of a marked decrease in the duration of post-reinforcement pausing, and consequent increase in the number of responses per interval; (b) a comparison of Figs. 31 and 33 with Figs. 20 and 22 also shows that these effects dissipated more rapidly when methylphenidate was in combination with reserpine than when the stimulant was administered alone, indicating an increased rate of metabolism of methylphenidate in a reserpinized animal.

Obviously, reserpine in combination with methylphenidate did not influence FI behavior in the same manner as reserpine alone. Again, the effect was a function of the schedule-dependent response rate of the individual subject under non-drug control conditions. Pre-reserpine control records (Fig. 29) show that, compared to the third and fifth periods, during the first 45 minute period W_4 performed at a relatively high level--short duration of post-reinforcement pausing and high response rate. The conclusion perforce must be that if the response rate generated by the schedule under non-drug, control conditions is high, rather than simply neutralizing each other, reserpine and methylphenidate interact in an extremely complex fashion.

This finding, which constitutes further evidence for the importance of the schedule in the control of behavior, is not without precedent. Dalrymple and Stretch (1967, in preparation) found that in reserpinized rats which under control conditions characteristically responded at a high rate on a tandem FI FR schedule, when methylphenidate was injected a greater degree of restoration of interval responding was apparent than in rats whose control rates of responding were low. With pigeons trained on a multiple FI FR schedule in a study by Smith (1964), small doses of d-Amphetamine restored normal rates and patterns of interval responding in reserpine-treated animals, and larger doses caused increases in rates which far surpassed rate increases attained in pigeons not treated with reserpine, "indicating a marked enhancement of the rate-increasing effect of d-Amphetamine by reserpine pretreatment." The mechanism was this--reserpine enhanced the rate-increasing effects of d-Amphetamine during the first part of the interval and antagonized the rate suppressant effects seen during the latter part of the interval. The importance of Smith's explanation is that it is directly applicable to the present study, since it is known that methylphenidate influences behavior in a manner similar to that of the amphetamines (Mechner and Latranyi, 1963).

Two further results of the reserpine-methylphenidate interaction deserve mention, although they are only distantly related, if at all. First, behavior in the reserpine phase which followed the reserpine-4 mg./Kg. methylphenidate series was characterized by a somewhat higher behavioral output than was observable during the initial series of reserpine-only administrations, indicating that high daily administrations of methylphenidate may reduce the effects of chronic reserpine treatment.

Second, it was apparent that after the first period of the session the effects of methylphenidate gradually became less pronounced, to the extent that even by the end of a 4 mg./Kg. session the reserpine syndrome was almost completely re-established. However, the fact that no convulsions ever occurred following a reserpine-methylphenidate session suggests a long-lasting though not overtly discernible effect of methylphenidate.

To summarize, it appears that in order for the reserpine-methylphenidate interaction to be adequately characterized a consideration of several factors is required:

(1) Chronic reserpine treatment results in a partial reduction of the FI pattern of responding, which is restored by methylphenidate;

(2) The degree of restoration varies directly with the methylphenidate dosage level;

(3) The degree of restoration is dependent also on the rate of responding characteristic of the individual animal under non-drug control conditions, i.e., recovery of responding is accelerated when the control rate is high;

(4) At the time of maximal action of methylphenidate, reserpine does not neutralize or antagonize, but rather augments the influence of the psychomotor stimulant, this effect of reserpine also being dependent on a high non-drug control rate of responding.

In conclusion it may be stated that, in addition to certain specific discoveries (for example, the temporally more pronounced effect of methylphenidate on duration of post-reinforcement pausing as compared to response rate), the single-most important finding to emerge from the

data of the present study is a further demonstration of the dependency of drug effects on control rates^{and patterns} of responding, a finding which justifies the author's re-emphasis of the constant necessity for a consideration of the interdependence of environmental, behavioral and pharmacological variables in the investigation of any drug-behavior interaction. To paraphrase Sidman (1959),

. . . the relations between drugs and behavior are a function not only of the drug but also of the conditions under which the behavior is generated.

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APPENDICES

DAILY RECORD OF W_1

Session	Parameters	Comments
1 (9/7/66)	training situation	
2	training situation	noise intensity 80 DB. shock intensity 2 mA. 2 hour sessions
3	training situation	
4	training situation	
5	training situation	
Bar Introduction		
6	FR 1 S ₁ -S ₂ 10 TO 30	5 hour sessions ↓
7	FR 1 S ₁ -S ₂ 10 TO 30	
8	FR 1 S ₁ -S ₂ 10 TO 30	
9	FR 1 S ₁ -S ₂ 10 TO 30	
10	FR 1 S ₁ -S ₂ 10 TO 30	
11	FR 1 S ₁ -S ₂ 10 TO 30	
Fixed-Ratio Transition		
12	FR 5 S ₁ -S ₂ 10 TO 30	
13	FR 5 S ₁ -S ₂ 10 TO 30	
14	FR 10 S ₁ -S ₂ 10 TO 30	
15	FR 15 S ₁ -S ₂ 20 TO 30	
16	FR 15 S ₁ -S ₂ 20 TO 30	
17	FR 20 S ₁ -S ₂ 20 TO 30	
18	FR 20 S ₁ -S ₂ 20 TO 30	
19	FR 25 S ₁ -S ₂ 20 TO 30	
20	FR 30 S ₁ -S ₂ 25 TO 30	
21	FR 30 S ₁ -S ₂ 25 TO 30	
22	FR 35 S ₁ -S ₂ 30 TO 30	
23	FR 45 S ₁ -S ₂ 40 TO 30	
24	FR 50 S ₁ -S ₂ 40 TO 30	
25	FR 50 S ₁ -S ₂ 40 TO 30	

Session	Parameters	Comments
26	FR 50 S_1-S_2 40 TO 30	
27	FR 55 S_1-S_2 50 TO 40	
28		not tested
29	FR 55 S_1-S_2 50 TO 40	
30	FR 60 S_1-S_2 50 TO 50	
31	FR 60 S_1-S_2 50 TO 50	
32	FR 70 S_1-S_2 55 TO 50	
33	FR 75 S_1-S_2 55 TO 50	
34	FR 80 S_1-S_2 55 TO 50	
35	FR 80 S_1-S_2 55 TO 50	
36	FR 85 S_1-S_2 55 TO 50	
37	FR 90 S_1-S_2 55 TO 50	
38	FR 90 S_1-S_2 55 TO 50	
39	FR 90 S_1-S_2 55 TO 50	
40	FR 90 S_1-S_2 55 TO 50	
41	FR 90 S_1-S_2 55 TO 50	
42	FR 90 S_1-S_2 55 TO 50	
43	FR 90 S_1-S_2 55 TO 50	
44	FR 90 S_1-S_2 55 TO 50	
45	FR 90 S_1-S_2 55 TO 50	
46		not tested
47	FR 100 S_1-S_2 65 TO 50	
48	FR 110 S_1-S_2 65 TO 60	
49	FR 120 S_1-S_2 70 TO 60	
50	FR 120 S_1-S_2 70 TO 60	
51	FR 125 S_1-S_2 70 TO 60	
52	FR 125 S_1-S_2 70 TO 60	
53	FR 125 S_1-S_2 70 TO 60	
54	FR 125 S_1-S_2 70 TO 60	
55	FR 125 S_1-S_2 70 TO 60	
56	FR 125 S_1-S_2 70 TO 60	

Session	Parameters	Comments
57	FR 130 S_1-S_2 70 TO 70	
58	FR 130 S_1-S_2 70 TO 70	
59	FR 140 S_1-S_2 80 TO 70	
60	FR 140 S_1-S_2 80 TO 70	
61	FR 140 S_1-S_2 80 TO 70	
62	FR 140 S_1-S_2 80 TO 70	
63	FR 140 S_1-S_2 80 TO 70	
64	FR 150 S_1-S_2 100 TO 100	
65	FR 150 S_1-S_2 100 TO 100	
66	FR 150 S_1-S_2 100 TO 100	
67	FR 150 S_1-S_2 100 TO 100	
68	FR 150 S_1-S_2 100 TO 100	
69	FR 150 S_1-S_2 100 TO 100	
70	FR 150 S_1-S_2 100 TO 100	
71	FR 150 S_1-S_2 100 TO 100	
72		not tested
73	FR 160 S_1-S_2 110 TO 110	
74	FR 160 S_1-S_2 110 TO 110	
75		not tested
76	FR 160 S_1-S_2 110 TO 110	
77	FR 170 S_1-S_2 120 TO 120	
78		not tested
79	FR 180 S_1-S_2 130 TO 120	
80	FR 180 S_1-S_2 130 TO 120	
81	FR 180 S_1-S_2 130 TO 120	
82	FR 190 S_1-S_2 130 TO 120	
83		not tested)
84		not tested)
85		not tested) program
86		not tested) changes
87		not tested)
88		not tested)

Session	Parameters	Comments
89	FR 190 S_1-S_2 150 TO 130	
90	FR 190 S_1-S_2 150 TO 130	
91	FR 300 S_1-S_2 180 TO 180	
92	FR 300 S_1-S_2 180 TO 180	
93	FR 300 S_1-S_2 180 TO 180	behavioral breakdown-session stopped
94	FR 50 S_1-S_2 90 TO 100	
95		not tested
96	FR 5 S_1-S_2 15 TO 30	
97	FR 5 S_1-S_2 10 TO 15	
98	FR 60 S_1-S_2 60 TO 60	4 hour sessions; 4 mA. shock intensity ↓
99	FR 100 S_1-S_2 90 TO 60	
100	FR 100 S_1-S_2 90 TO 60	
101	FR 300 S_1-S_2 180 TO 180	behavioral breakdown-session stopped
102	FR 150 S_1-S_2 120 TO 100	
103	FR 150 S_1-S_2 120 TO 100	
104	FR 200 S_1-S_2 150 TO 130	
105	FR 220 S_1-S_2 160 TO 140	
106		not tested
107	FR 220 S_1-S_2 160 TO 140	
108	FR 230 S_1-S_2 160 TO 145	
109	FR 250 S_1-S_2 180 TO 180	final parameters
110		not tested
111	FR 250 S_1-S_2 180 TO 180	shock intensity 12 mA. ↓
112	FR 250 S_1-S_2 180 TO 180	
113	FR 250 S_1-S_2 180 TO 180	
114		not tested
115	FR 250 S_1-S_2 180 TO 180	
116	FR 250 S_1-S_2 180 TO 180	
117	FR 250 S_1-S_2 180 TO 180	
118	FR 250 S_1-S_2 180 TO 180	
119	FR 250 S_1-S_2 180 TO 180	

Session	Parameters	Comments
120	FR 250 S_1-S_2 180 TO 180	
121	FR 250 S_1-S_2 180 TO 180	
122		not tested
123	FR 250 S_1-S_2 180 TO 180	
124	FR 250 S_1-S_2 180 TO 180	
125	FR 250 S_1-S_2 180 TO 180	
126	FR 250 S_1-S_2 180 TO 180	
127		not tested
128	FR 250 S_1-S_2 180 TO 180	

Stabilization at Final Parameters

129	FR 250 S_1-S_2 TO 180	225 minute sessions
130	FR 250 S_1-S_2 TO 180	1 c.c. saline I.P. ↓
131	FR 250 S_1-S_2 TO 180	
132	FR 250 S_1-S_2 TO 180	
133	FR 250 S_1-S_2 TO 180	-shock generator mal- function → extinction
134	FR 250 S_1-S_2 TO 180	-restabilization fol- lowing extinction
135	FR 250 S_1-S_2 TO 180	1 c.c. saline I.P.
136	FR 250 S_1-S_2 TO 180	
137	FR 250 S_1-S_2 TO 180	
138		not tested
139	FR 250 S_1-S_2 180 TO 180	
140	FR 250 S_1-S_2 180 TO 180	
141	FR 250 S_1-S_2 180 TO 180	

Methylphenidate Dose-Effect Series

142	1 mg./Kg.
143	Control
144	1
145	C
146	2
147	C

Session	Parameters	Comments
148	1	
149	C	
150	2	
151	C	
152	2	
153	C	
154		not tested
155	C	
156	4	lever failure- session stopped
157	C	
158	4	
159	C	
160	1	
161		not tested
162	C	
163	4	
164	C	
165	1	
166	C	
167	2	
168	C	
169	4	
170		not tested
171		not tested
172	C	
173	2	
174	C	
175	4	
176	C	
177	C	
178	C	
179	4	

Session	Parameters	Comments
Restabilization at Reduced Parameters (FR 50 S ₁ -S ₂ 60 TO 60) shock intensity 6 mA.		
180	FR 50 S ₁ -S ₂ 60 TO 60	↓
181	FR 50 S ₁ -S ₂ 60 TO 60	
182	FR 50 S ₁ -S ₂ 60 TO 60	
183	FR 50 S ₁ -S ₂ 60 TO 60	
184	FR 50 S ₁ -S ₂ 60 TO 60	
185	FR 50 S ₁ -S ₂ 60 TO 60	
186	FR 50 S ₁ -S ₂ 60 TO 60	
187	FR 50 S ₁ -S ₂ 60 TO 60	
188	FR 50 S ₁ -S ₂ 60 TO 60	
189	FR 50 S ₁ -S ₂ 60 TO 60	

Methylphenidate Dose-Effect Series at Reduced Parameters

190	2	
191	C	
192	1	
193	C	
194	2	
195	C	
196	2	
197	C	
198	4	S's foot caught in grid--shock-induced unconsciousness; session stopped
199		not tested
200		not tested
201		not tested
202		not tested
203		not tested
204		not tested
205	C	
206	C	

Session	Parameters	Comments
207	C	
208	1	lever failure
209		not tested
210		not tested
211	C	
212	C	
213	C	
214	1	
215	C	behavioral breakdown-session stopped
216	C	
217	C	
218	C	
219		not tested
220	C	
221		not tested-1 mg./Kg. methyl-phenidate administered
222	C	
223	2	
224	C	
225	4	
226	C	
227		not tested
228	C	
229	C	
230	2	
231	C	
232	4	
233	C	
234	1	
235	C	
236	2	
237	C	

Session	Parameters	Comments
238	4	
239	C	
240	1	
241	C	
242	4	
243	C	
244	1	
245	C	
246	4	
247		not tested
248	C	
249	1	
250	C	
251	1	
252	C	
253 (18/3/67)	2	

DAILY RECORD OF W_2

Session	Parameters	Comments
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Fixed-Ratio Transition

1 (3/8/66)	FR 1 S_1-S_2 10 TO 20	5 hour sessions noise intensity 80 DB. shock intensity 2 mA. ↓
2	FR 1 S_1-S_2 10 TO 20	
3	FR 2 S_1-S_2 10 TO 20	
4	FR 4 S_1-S_2 10 TO 30	
5	FR 5 S_1-S_2 10 TO 30	
6	FR 10 S_1-S_2 10 TO 30	
7	FR 15 S_1-S_2 10 TO 30	
8	FR 25 S_1-S_2 20 TO 30	
9	FR 30 S_1-S_2 20 TO 30	
10	FR 45 S_1-S_2 35 TO 35	
11	FR 50 S_1-S_2 35 TO 35	
12	FR 55 S_1-S_2 40 TO 40	
13		
14	FR 60 S_1-S_2 40 TO 40	
15	FR 70 S_1-S_2 50 TO 50	
16	FR 80 S_1-S_2 50 TO 50	
17	FR 90 S_1-S_2 55 TO 50	
18	FR 95 S_1-S_2 60 TO 60	
19	FR 100 S_1-S_2 60 TO 60	
20	FR 110 S_1-S_2 65 TO 60	
21	FR 115 S_1-S_2 70 TO 60	
22	FR 115 S_1-S_2 70 TO 60	
23	FR 120 S_1-S_2 70 TO 60	
24	FR 130 S_1-S_2 70 TO 65	
25	FR 140 S_1-S_2 80 TO 70	
26	FR 150 S_1-S_2 85 TO 75	
27	FR 160 S_1-S_2 90 TO 80	

Session	Parameters	Comments
28	FR 170 S_1-S_2 95 TO 85	
29	FR 180 S_1-S_2 95 TO 85	equipment malfunction- session stopped
30	FR 180 S_1-S_2 95 TO 85	
31	FR 180 S_1-S_2 95 TO 85	lever jammed-1 hr. steady shock-session stopped
32		not tested
33	FR 180 S_1-S_2 95 TO 85	
34	FR 190 S_1-S_2 100 TO 90	
35	FR 200 S_1-S_2 105 TO 100	
36	FR 210 S_1-S_2 110 TO 110	
37	FR 210 S_1-S_2 110 TO 110	
38	FR 220 S_1-S_2 115 TO 115	
39	FR 220 S_1-S_2 115 TO 115	
40	FR 220 S_1-S_2 115 TO 115	
41	FR 220 S_1-S_2 115 TO 115	
42	FR 225 S_1-S_2 120 TO 130	
43	FR 230 S_1-S_2 120 TO 130	
44	FR 230 S_1-S_2 120 TO 130	
45	FR 230 S_1-S_2 120 TO 130	
46	FR 240 S_1-S_2 125 TO 135	
47	FR 250 S_1-S_2 130 TO 145	
48		not tested
49	FR 250 S_1-S_2 130 TO 145	
50		not tested
51	FR 250 S_1-S_2 130 TO 145	
52	FR 260 S_1-S_2 135 TO 150	
53	FR 260 S_1-S_2 140 TO 150	
54	FR 270 S_1-S_2 150 TO 150	
55	FR 280 S_1-S_2 160 TO 160	
56		not tested)
57		not tested) program changes
58		not tested)

Session	Parameters	Comments
59		not tested)
60		not tested) program changes
61	FR 280 S_1-S_2 180 TO 160	
62	FR 280 S_1-S_2 180 TO 165	
63	FR 290 S_1-S_2 180 TO 170	
64	FR 300 S_1-S_2 180 TO 180	
65		not tested
66	FR 300 S_1-S_2 180 TO 180	
67	FR 300 S_1-S_2 180 TO 180	
68		not tested
69	FR 300 S_1-S_2 180 TO 180	
70		not tested
71	FR 300 S_1-S_2 180 TO 180	4 hr. sessions; shock intensity 4 mA. ↓
72	FR 300 S_1-S_2 180 TO 180	
73		not tested
74	FR 300 S_1-S_2 180 TO 180	
75	FR 300 S_1-S_2 180 TO 180	
76		not tested
77	FR 300 S_1-S_2 180 TO 180	
78		not tested
79	FR 300 S_1-S_2 180 TO 180	
80	FR 300 S_1-S_2 180 TO 180	
81	FR 250 S_1-S_2 180 TO 180	final parameters
82		not tested
83		not tested
84	FR 250 S_1-S_2 180 TO 180	shock intensity 12 mA. ↓
85	FR 250 S_1-S_2 180 TO 180	
86	FR 250 S_1-S_2 180 TO 180	
87	FR 250 S_1-S_2 180 TO 180	
88	FR 250 S_1-S_2 180 TO 180	
89	FR 250 S_1-S_2 180 TO 180	

Appendix 1 (b) continued

Session	Parameters	Comments
90	FR 250 S ₁ -S ₂ 180 TO 180	
91	FR 250 S ₁ -S ₂ 180 TO 180	
92	FR 250 S ₁ -S ₂ 180 TO 180	
93	FR 250 S ₁ -S ₂ 180 TO 180	
94	FR 250 S ₁ -S ₂ 180 TO 180	
95		not tested
96	FR 250 S ₁ -S ₂ 180 TO 180	
97	FR 250 S ₁ -S ₂ 180 TO 180	
98		not tested
99	FR 250 S ₁ -S ₂ 180 TO 180	no data
100		not tested
101	FR 250 S ₁ -S ₂ 180 TO 180	
Stabilization at Final Parameters		
102	FR 250 S ₁ -S ₂ 180 TO 180	1 c.c. saline; 225 min. sessions
103	FR 250 S ₁ -S ₂ 180 TO 180	1 c.c. saline
104	FR 250 S ₁ -S ₂ 180 TO 180	no saline
105	FR 250 S ₁ -S ₂ 180 TO 180	no saline
106		not tested-shock generator malfunction
107	FR 250 S ₁ -S ₂ 180 TO 180	
108	FR 250 S ₁ -S ₂ 180 TO 180	1 c.c. saline
109	FR 250 S ₁ -S ₂ 180 TO 180	1 c.c. saline
110	FR 250 S ₁ -S ₂ 180 TO 180	no saline
111	FR 250 S ₁ -S ₂ 180 TO 180	no saline
112	FR 250 S ₁ -S ₂ 180 TO 180	no saline
Methylphenidate Dose-Effect Series		
113	8 mg./Kg.	
114	Control	behavioral breakdown
115		not tested
116		not tested

Session	Parameters	Comments
117	Control	
118	2 mg./Kg.	
119	C	
120	1	
121	C	
122	C	
123	2	
124	C	
125	1	lever failure-session stopped
126	C	
127	1	
128	C	
129	4	
130	C	
131	4	
132	C	
133		not tested
134	2	
135	C	
136	4	
137	C	
138	1	
139	C	
140	2	
141	C	
142	4	
143	C	
144	2	
145	C	
146	1	
147	C	

Appendix 1 (b) continued

Session	Parameters	Comments
148	4	
149	C	
150	1	
Methylphenidate Time Course Series		
151	2-90	
152	C-90	
153	4-180	
154	C-180	
155	2-90	
156	C-90	
157	1-90	
158	C-180	
159	1-90	
160	C-90	
161	4-90	
162	C-180	
163		not tested
164		not tested
165		not tested
166		not tested
167	C-180	
168	C	
169	C-180	
170	C	
171	C	
172	C	
173	1-180	

Appendix 1 (b) continued

Session	Parameters	Comments
Restabilization at Reduced Parameters (FR 100 S_1-S_2 120 TO 120)		
174	FR 100 S_1-S_2 120 TO 120	
175	FR 100 S_1-S_2 120 TO 120	
176	FR 100 S_1-S_2 120 TO 120	
177	FR 100 S_1-S_2 120 TO 120	
178	FR 100 S_1-S_2 120 TO 120	
179	FR 100 S_1-S_2 120 TO 120	
180	FR 100 S_1-S_2 120 TO 120	
181	FR 100 S_1-S_2 120 TO 120	
182	FR 100 S_1-S_2 120 TO 120	
183	FR 100 S_1-S_2 120 TO 120	
184	FR 100 S_1-S_2 120 TO 120	
185	FR 100 S_1-S_2 120 TO 120	
Methylphenidate Time Course Series at Reduced Parameters		
186	1-180	
187	C-90	
188	C-90	
189	1-90	
190	C-180	
191	2-180	shock intensity set too low
192	2-180	
193	C-90	behavioral breakdown-session stopped
194	C	
195	C-90	
196	1-90	
197	C-180	
198	2-90	
199		not tested
200	C-90	
201	2-180	

Session	Parameters	Comments
202	C	
203	C-180	
204	4-180	
205	C-90	
206		not tested
207	2-180	
208	C-180	
209	4-90	
210	C-90	
211	2-90	
212	C-180	
213	4-180	
214		not tested
215	C-90	
216	4-90	
217	C-180	
218	1-180	
219	C-180	
220	1-90	
221	C-90	
222	4-90	
223	C-180	
224	4-180	
225	C-90	
226	1-180	
227	C-180	
228	2-90	
229	C-90	
230	1-90	
231 (29/3/67)	C-180	

DAILY RECORD OF W_3

Session	Parameters	Comments
1 (9/7/66)	training situation	
2	training situation	noise intensity 80 DB. shock intensity 2 mA. 2 hour sessions
3	training situation	
4	training situation	
5	training situation	
Bar Introduction		
6	FR 1 S ₁ -S ₂ 10 TO 30	5 hour sessions ↓
7	FR 1 S ₁ -S ₂ 10 TO 30	
8	FR 1 S ₁ -S ₂ 10 TO 30	
9	FR 1 S ₁ -S ₂ 10 TO 30	
10	FR 1 S ₁ -S ₂ 10 TO 30	
11	FR 1 S ₁ -S ₂ 10 TO 30	
Fixed-Interval Transition		
12	FI 10 LH 10 TO 30	
13	FI 15 LH 10 TO 30	
14	FI 20 LH 10 TO 30	
15	FI 20 LH 10 TO 30	
16	FI 30 LH 10 TO 30	
17	FI 30 LH 10 TO 30	
18	FI 40 LH 10 TO 30	
19	FI 40 LH 10 TO 30	
20	FI 50 LH 10 TO 30	
21	FI 60 LH 10 TO 30	
22	FI 60 LH 10 TO 30	
23	FI 60 LH 10 TO 30	
24	FI 60 LH 10 TO 30	
25	FI 60 LH 10 TO 30	

Appendix 1 (c) continued

Session	Parameters	Comments
26	FI 60 LH 5 TO 30	
27	FI 60 LH 5 TO 30	
28		not tested - injury to tail
29		not tested - injury to tail
30	FI 60 LH 5 TO 45	
31	FI 60 LH 5 TO 45	
32	FI 60 LH 5 TO 45	
33	FI 60 LH 5 TO 45	
34	FI 60 LH 3 TO 45	
35	FI 60 LH 3 TO 45	
36	FI 60 LH 3 TO 45	
37	FI 60 LH 3 TO 45	
38	FI 60 LH 3 TO 45	
39	FI 60 LH 2 TO 45	
40	FI 60 LH 2 TO 45	
41	FI 60 LH 2 TO 45	
42	FI 60 LH 2 TO 45	
43	FI 60 LH 2 TO 45	
44	FI 70 LH 2 TO 45	
45	FI 70 LH 2 TO 45	
46	FI 90 LH 2 TO 60	
47	FI 90 LH 2 TO 60	
48	FI 110 LH 2 TO 70	
49	FI 110 LH 2 TO 70	
50	FI 110 LH 2 TO 70	
51	FI 110 LH 2 TO 70	
52	FI 110 LH 2 TO 70	
53	FI 110 LH 2 TO 70	
54	FI 120 LH 2 TO 70	
55	FI 120 LH 2 TO 70	
56	FI 130 LH 2 TO 70	

Session	Parameters	Comments
57	FI 130 LH 2 TO 70	
58	FI 140 LH 2 TO 80	
59	FI 140 LH 2 TO 80	
60	FI 140 LH 2 TO 80	
61	FI 140 LH 2 TO 80	
62	FI 140 LH 2 TO 90	
63	FI 140 LH 2 TO 70	
64	FI 140 LH 2 TO 70	
65	FI 140 LH 2 TO 70	
66	FI 140 LH 2 TO 70	
67	FI 150 LH 2 TO 100	
68	FI 150 LH 2 TO 100	
69	FI 150 LH 2 TO 110	lever jammed-session stopped after 4 hours
70	FI 150 LH 2 TO 110	
71	FI 150 LH 2 TO 110	
72		not tested
73		not tested
74	FI 150 LH 2 TO 110	
75	FI 180 LH 2 TO 180	final parameters
76	FI 180 LH 2 TO 180	
77	FI 180 LH 2 TO 180	
78	FI 180 LH 2 TO 180	
79	FI 180 LH 2 TO 180	
80		not tested)
81		not tested)
82		not tested) program changes
83		not tested)
84		not tested)
85		not tested)
86	FI 180 LH 2 TO 180	warmup at reduced parameters
87	FI 180 LH 2 TO 180	warmup at reduced parameters

Appendix 1 (c) continued

Session	Parameters	Comments
88	FI 180 LH 2 TO 180	
89	FI 180 LH 2 TO 180	
90	FI 180 LH 2 TO 180	
91	FI 180 LH 2 TO 180	
92	FI 180 LH 2 TO 180	
93	FI 180 LH 2 TO 180	
94	FI 180 LH 2 TO 180	4 hour sessions; shock intensity 4 mA. ↓
95	FI 180 LH 2 TO 180	
96	FI 180 LH 2 TO 180	
97	FI 180 LH 2 TO 180	
98	FI 180 LH 2 TO 180	
99	FI 180 LH 2 TO 180	
100	FI 180 LH 2 TO 180	
101	FI 180 LH 2 TO 180	
102	FI 180 LH 2 TO 180	
103	FI 180 LH 2 TO 180	
104	FI 180 LH 2 TO 180	
105	FI 180 LH 2 TO 180	
106		not tested
107	FI 180 LH 2 TO 180	shock intensity 12 mA. ↓
108	FI 180 LH 2 TO 180	
109	FI 180 LH 2 TO 180	
110	FI 180 LH 2 TO 180	
111	FI 180 LH 2 TO 180	
112	FI 180 LH 2 TO 180	
113	FI 180 LH 2 TO 180	
114	FI 180 LH 2 TO 180	
115	FI 180 LH 2 TO 180	
116	FI 180 LH 2 TO 180	
117	FI 180 LH 2 TO 180	
118	FI 180 LH 2 TO 180	

Appendix 1 (c) continued

Session	Parameters	Comments
119	FI 180 LH 2 TO 180	
120	FI 180 LH 2 TO 180	
121	FI 180 LH 2 TO 180	
122	FI 180 LH 2 TO 180	
123		not tested
124	FI 180 LH 2 TO 180	

Stabilization at Final Parameters

125	FI 180 LH 2 TO 180	225 minute sessions	↓
126	FI 180 LH 2 TO 180	1 c.c. saline	
127	FI 180 LH 2 TO 180	no saline	
128	FI 180 LH 2 TO 180	no saline	
129	FI 180 LH 2 TO 180	no saline	
130	FI 180 LH 2 TO 180	1 c.c. saline	
131	FI 180 LH 2 TO 180	no saline	
132	FI 180 LH 2 TO 180	1 c.c. saline	
133	FI 180 LH 2 TO 180	behavioral breakdown session stopped; no saline	
134		not tested	
135		not tested	
136	FI 180 LH 2 TO 180	no saline	
137	FI 180 LH 2 TO 180	no saline	

Methylphenidate Dose-Effect Series

138	8 mg./Kg.	
139	Control	
140		not tested
141	C	
142	1	
143	C	behavioral breakdown-session stopped
144	C	
145	2	

Session	Parameters	Comments
146	C	
147	C	
148	1	
149	C	
150	C	
151		not tested
152	C	
153	2	
154	C	
155	4	emesis
156	C	
157	2	
158	C	
159	4	emesis
160	C	
161	1	
162	C	
163	4	emesis
164	C	
165	1	
166	C	
167	C	
168	2	
169	C	
170	4	
171	C	
172	1	
173	C	
174	C	
175	2	
176	C	

Appendix 1 (c) continued

Session	Parameters	Comments
177	4	
178	C	
179	C	
Methylphenidate Time Course Series		
180	2-90	
181	C-90	
182	4-180	
183	C-180	
184	2-90	
185	C-90	
186	1-90	
187	C-180	
188	1-90	
189	C-90	
190	4-90	
191	C-180	
192	4-90	
193	C-90	
194		not tested
195	2-180	
196	C-180	
197	4-90	
198	C-90	
199	2-180	
200	C-90	
201	2-180	
202	C-90	
203	4-180	
204	C-180	
205	1-90	
206	C-90	

Session	Parameters	Comments
207	2-90	
208		not tested
209	C-180	
210	1-180	
211	C-180	
212		not tested
213	1-180	
214	C-180	
215	1-180	
216	C-90	
217	4-180	
218	C-180	
219		not tested)
220		not tested) rest days
221		not tested)

Pre-Reserpine Stabilization at Final Parameters

222	FI 180 LH 2 TO 180
223	FI 180 LH 2 TO 180
224	FI 180 LH 2 TO 180
225	FI 180 LH 2 TO 180
226	FI 180 LH 2 TO 180

Reserpine Administrations

227	.05 mg./Kg. 20 hours prior
228	.05 mg./Kg. 20 hours prior
229	.05 mg./Kg. 20 hours prior
230	.1 mg./Kg. 20 hours prior
231	.1 mg./Kg. 20 hours prior
232	.2 mg./Kg. 20 hours prior
233	.2 mg./Kg. 20 hours prior
234	.2 mg./Kg. 20 hours prior

Session	Parameters	Comments
235	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours post-injection
236	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours post-injection
237	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours post-injection
238	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours post-injection
239	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours post-injection
240	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours post-injection
241	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours post-injection
242	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours post-injection
243	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours post-injection
244	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours post-injection

Reserpine-Methylphenidate Administrations

245	.3 mg./Kg. Reserpine 20 hours prior / 2 mg./Kg. Methylphenidate	no convulsions
246	.3 mg./Kg. Reserpine 20 hours prior / 2 mg./Kg. Methylphenidate	no convulsions
247	.3 mg./Kg. Reserpine 20 hours prior / 2 mg./Kg. Methylphenidate	no convulsions
248	.3 mg./Kg. Reserpine 20 hours prior / 2 mg./Kg. Methylphenidate	no convulsions
249	.3 mg./Kg. Reserpine 20 hours prior / 2 mg./Kg. Methylphenidate	no convulsions

Reserpine Only (a)

250	.3 mg./Kg. Reserpine 20 hours prior	convulsions
251	.3 mg./Kg. Reserpine 20 hours prior	convulsions
252	.3 mg./Kg. Reserpine 20 hours prior	convulsions

Session	Parameters	Comments
253	.3 mg./Kg. Reserpine 20 hours prior	convulsions
254	.3 mg./Kg. Reserpine 20 hours prior	convulsions

Reserpine-Methylphenidate Administrations

255 (25/3/67)	.3 mg./Kg. Reserpine 20 hours prior / 4 mg./Kg. Methylphenidate	Death c. 45 minutes from session start
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DAILY RECORD OF W_4

Session	Parameters	Comments
1 (9/7/66)	training situation	
2	training situation	noise intensity 80 DB. shock intensity 2 mA. 2 hour sessions
3	training situation	
4	training situation	
5	training situation	
Bar Introduction		
6	FR 1 S_1-S_2 10 TO 30	5 hour sessions ↓
7	FR 1 S_1-S_2 10 TO 30	
8	FR 1 S_1-S_2 10 TO 30	
9	FR 1 S_1-S_2 10 TO 30	
10	FR 1 S_1-S_2 10 TO 30	
11	FR 1 S_1-S_2 10 TO 30	
Fixed-Interval Transition		
12	FI 10 LH 10 TO 30	
13	FI 15 LH 10 TO 30	
14	FI 20 LH 10 TO 30	
15	FI 20 LH 10 TO 30	
16	FI 30 LH 10 TO 30	
17	FI 40 LH 10 TO 30	
18	FI 40 LH 10 TO 30	
19		not tested
20	FI 40 LH 10 TO 30	
21	FI 50 LH 10 TO 30	
22	FI 60 LH 10 TO 30	
23	FI 60 LH 10 TO 30	
24	FI 60 LH 10 TO 30	
25	FI 60 LH 10 TO 30	

Session	Parameters	Comments
26	FI 60 LH 10 TO 30	
27	FI 60 LH 5 TO 30	
28	FI 60 LH 5 TO 30	
29	FI 60 LH 2 TO 45	
30	FI 60 LH 5 TO 45	
31	FI 60 LH 5 TO 45	
32	FI 60 LH 5 TO 45	
33	FI 60 LH 5 TO 45	
34	FI 60 LH 3 TO 45	
35	FI 60 LH 3 TO 45	
36	FI 60 LH 3 TO 45	
37	FI 60 LH 3 TO 45	
38	FI 60 LH 3 TO 45	
39	FI 60 LH 2 TO 45	
40	FI 60 LH 2 TO 45	
41	FI 60 LH 2 TO 45	
42	FI 60 LH 2 TO 45	
43	FI 60 LH 2 TO 45	
44	FI 60 LH 2 TO 45	
45	FI 70 LH 2 TO 45	
46	FI 90 LH 2 TO 60	
47	FI 90 LH 2 TO 60	
48	FI 90 LH 2 TO 60	
49	FI 110 LH 2 TO 70	
50	FI 110 LH 2 TO 70	
51	FI 120 LH 2 TO 70	
52	FI 120 LH 2 TO 70	
53	FI 130 LH 2 TO 70	
54	FI 140 LH 2 TO 80	
55	FI 150 LH 2 TO 80	
56	FI 160 LH 2 TO 80	

Session	Parameters	Comments
57	FI 170 LH 2 TO 85	
58	FI 170 LH 2 TO 85	
59	FI 170 LH 2 TO 85	
60	FI 170 LH 2 TO 85	
61	FI 175 LH 2 TO 100	
62	FI 175 LH 2 TO 100	
63	FI 175 LH 2 TO 100	
64	FI 175 LH 2 TO 100	
65	FI 175 LH 2 TO 100	
66	FI 178 LH 2 TO 140	
67	FI 178 LH 2 TO 140	
68	FI 178 LH 2 TO 150	
69	FI 178 LH 2 TO 160	
70	FI 178 LH 2 TO 170	
71	FI 178 LH 2 TO 180	
72		not tested
73		not tested
74		not tested
75	FI 180 LH 2 TO 180	
76	FI 180 LH 2 TO 180	
77	FI 180 LH 2 TO 180	
78	FI 180 LH 2 TO 180	
79	FI 180 LH 2 TO 180	
80		not tested)
81		not tested)
82		not tested)
83		not tested) program changes
84		not tested)
85		not tested)
86		not tested)
87	FI 180 LH 2 TO 180	

Appendix 1 (d) continued

Session	Parameters	Comments
88	FI 180 LH 2 TO 180	
89	FI 180 LH 2 TO 180	
90	FI 180 LH 2 TO 180	
91	FI 180 LH 2 TO 180	
92	FI 180 LH 2 TO 180	
93	FI 180 LH 2 TO 180	
94	FI 180 LH 2 TO 180	
95	FI 180 LH 2 TO 180	
96	FI 180 LH 2 TO 180	4 hour sessions; shock intensity 4 mA.
97	FI 180 LH 2 TO 180	
98	FI 180 LH 2 TO 180	
99	FI 180 LH 2 TO 180	
100	FI 180 LH 2 TO 180	
101	FI 180 LH 2 TO 180	
102	FI 180 LH 2 TO 180	
103		not tested
104	FI 180 LH 2 TO 180	
105	FI 180 LH 2 TO 180	
106		not tested
107	FI 180 LH 2 TO 180	shock intensity 12 mA.
108	FI 180 LH 2 TO 180	
109	FI 180 LH 2 TO 180	
110	FI 180 LH 2 TO 180	
111	FI 180 LH 2 TO 180	
112	FI 180 LH 2 TO 180	
113	FI 180 LH 2 TO 180	
114	FI 180 LH 2 TO 180	
115	FI 180 LH 2 TO 180	
116	FI 180 LH 2 TO 180	
117	FI 180 LH 2 TO 180	
118	FI 180 LH 2 TO 180	

Session	Parameters	Comments
119	FI 180 LH 2 TO 180	
120	FI 180 LH 2 TO 180	
121	FI 180 LH 2 TO 180	
122	FI 180 LH 2 TO 180	
123		not tested
124	FI 180 LH 2 TO 180	
Stabilization at Final Parameters		
125	FI 180 LH 2 TO 180	225 minute sessions
126	FI 180 LH 2 TO 180	1 c.c. saline
127		not tested)
128		not tested)
129		not tested) ill
130		not tested)
131		not tested)
132	FI 180 LH 2 TO 180	
133	FI 180 LH 2 TO 180	
134	FI 180 LH 2 TO 180	
135	FI 180 LH 2 TO 180	
136	FI 180 LH 2 TO 180	
137	FI 180 LH 2 TO 180	
138	FI 180 LH 2 TO 180	
139	FI 180 LH 2 TO 180	

Methylphenidate Dose-Effect Series

140	1 mg./Kg.
141	Control
142	2
143	C
144	1
145	C

Session	Parameters	Comments
146	2	
147	C	
148	2	
149	C	
150		not tested
151	C	
152	1	
153	C	
154	4	
155	C	
156	C	
157	2	
158	C	
159	4	
160	C	
161	1	
162	C	
163	4	
164	C	
165	4	
166		not tested
167		not tested
168	C	
169	2	
170	C	
171	1	
172	C	
173	4	
174	C	
175	C	
176	C	

Session	Parameters	Comments
Reserpine Administrations		
177	.2 mg./Kg. 20 hours prior	
178	C; .2 mg./Kg. Methyl-phenidate after 180 minutes	session 225 + 45 = 270 minutes
179		not tested
180	C	
181	C	
182		not tested
Convalescence due to Broken Left Forearm (radius and ulna)		
183		not tested
184		not tested
185		not tested
186		not tested
187		not tested
188		not tested
189		not tested
190		not tested
191		not tested
192		not tested
193		not tested
194		not tested
195		not tested
196		not tested
197		not tested
198		not tested
199		not tested
200		not tested
201		not tested
202		not tested
203		not tested

Session	Parameters	Comments
204		not tested
205		not tested
206		not tested
207		not tested
208		not tested
209		not tested
210		not tested
211		not tested
212		not tested
213		not tested
214		not tested
215		not tested
216		not tested

Post-Fracture, Pre-Reserpine Stabilization at Final Parameters

217	FI 180 LH 2 TO 180
218	FI 180 LH 2 TO 180
219	FI 180 LH 2 TO 180
220	FI 180 LH 2 TO 180
221	FI 180 LH 2 TO 180

Reserpine Administrations

222	.05 mg./Kg. 20 hours prior
223	.05 mg./Kg. 20 hours prior
224	.05 mg./Kg. 20 hours prior
225	.05 mg./Kg. 20 hours prior
226	.1 mg./Kg. 20 hours prior
227	.1 mg./Kg. 20 hours prior
228	.1 mg./Kg. 20 hours prior
229	.2 mg./Kg. 20 hours prior
230	.2 mg./Kg. 20 hours prior

Session	Parameters	Comments
231	.2 mg./Kg. 20 hours prior	
232	.2 mg./Kg. 20 hours prior	
233	.2 mg./Kg. 20 hours prior	
234	.2 mg./Kg. 20 hours prior	
235	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours after injection
236	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours after injection
237	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours after injection
238	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours after injection
239	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours after injection
240	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours after injection
241	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours after injection
242	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours after injection
243	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours after injection
244	.3 mg./Kg. 20 hours prior	Parkinson-like convulsions 4 - 8 hours after injection

Reserpine-Methylphenidate Administrations

245	.3 mg./Kg. Reserpine 20 hours prior; 2 mg./Kg. Methylphenidate	no convulsions
246	.3 mg./Kg. Reserpine 20 hours prior; 2 mg./Kg. Methylphenidate	no convulsions
247	.3 mg./Kg. Reserpine 20 hours prior; 2 mg./Kg. Methylphenidate	no convulsions
248	.3 mg./Kg. Reserpine 20 hours prior; 2 mg./Kg. Methylphenidate	no convulsions
249	.3 mg./Kg. Reserpine 20 hours prior; 2 mg./Kg. Methylphenidate	no convulsions

Session	Parameters	Comments
Reserpine Only (a)		
250	.3 mg./Kg. Reserpine 20 hours prior	convulsions
251	.3 mg./Kg. Reserpine 20 hours prior	convulsions
252	.3 mg./Kg. Reserpine 20 hours prior	convulsions
253	.3 mg./Kg. Reserpine 20 hours prior	convulsions
254	.3 mg./Kg. Reserpine 20 hours prior	convulsions
Reserpine-Methylphenidate Administrations		
255	.3 mg./Kg. Reserpine 20 hours prior / 4 mg./Kg. Methylphenidate	no convulsions
256	.3 mg./Kg. Reserpine 20 hours prior / 4 mg./Kg. Methylphenidate	no convulsions
257	.3 mg./Kg. Reserpine 20 hours prior / 4 mg./Kg. Methylphenidate	no convulsions
258	.3 mg./Kg. Reserpine 20 hours prior / 4 mg./Kg. Methylphenidate	no convulsions
259	.3 mg./Kg. Reserpine 20 hours prior / 4 mg./Kg. Methylphenidate	no convulsions
Reserpine Only (b)		
260	.3 mg./Kg. Reserpine 20 hours prior	no convulsions
261	.3 mg./Kg. Reserpine 20 hours prior	no convulsions
262	.3 mg./Kg. Reserpine 20 hours prior	prolonged convulsions
263	.3 mg./Kg. Reserpine 20 hours prior	short convulsion period
264 (31/3/67)	.3 mg./Kg. Reserpine 20 hours prior	

Table 1

 W_1 and W_2

Mean shock rates per hour for: (a) W_1 during the Methylphenidate Dose-Effect series on both FR 250 and FR 50;
 (b) W_2 during the Methylphenidate Dose-Effect series on FR 250; and (c) W_2 during the Methylphenidate Time Course series on FR 250.

(a)

W_1		FR 250	FR 50
Control	1	6.44	0.67
	3	8.89	1.20
	5	9.41	3.20
1 mg./Kg.	1	5.06	0.80
	3	5.07	0.80
	5	7.20	2.40
2 mg./Kg.	1	12.00	28.66
	3	3.73	0.00
	5	3.20	1.33
4 mg./Kg.	1	16.26	53.00
	3	11.20	15.00
	5	10.66	0.44

(b)

W_2		FR 250
Control	1	0.93
	3	1.06
	5	1.20
1 mg./Kg.	1	3.46
	3	1.87
	5	0.00
2 mg./Kg.	1	5.33
	3	1.60
	5	0.00
4 mg./Kg.	1	8.27
	3	4.27
	5	0.00

(c)

W_2		FR 250
Control 90	1	0.83
	3	0.00
	5	0.50
Control 180	1	1.86
	3	0.61
	5	0.40
1 mg./Kg. 90	1	0.00
	3	0.00
	5	0.00
1 mg./Kg. 180	1	0.00
	3	0.00
	5	0.00
2 mg./Kg. 90	1	3.55
	3	0.00
	5	0.00
2 mg./Kg. 180	1	0.00
	3	0.00
	5	0.89
4 mg./Kg. 90	1	12.44
	3	0.00
	5	0.44
4 mg./Kg. 180	1	0.44
	3	0.44
	5	0.00

Table 2

 W_3

Mean shock rates per hour for: (a) W_3 during the Methylphenidate Dose-Effect series on FI 180 LH 2; and (b) W_3 during the Methylphenidate Time Course series on FI 180 LH 2.

(a)

W_3		FI 180 LH 2
Control	1	1.46
	3	1.46
	5	1.46
1 mg./Kg.	1	1.06
	3	0.00
	5	0.27
2 mg./Kg.	1	1.33
	3	2.39
	5	0.27
4 mg./Kg.	1	3.46
	3	2.39
	5	1.60

(b)

W_3		FI 180 LH 2
Control 90	1	1.33
	3	1.71
	5	1.95
Control 180	1	0.95
	3	1.52
	5	1.71
1 mg./Kg. 90	1	0.00
	3	0.00
	5	0.44
1 mg./Kg. 180	1	0.44
	3	0.00
	5	1.33
2 mg./Kg. 90	1	1.78
	3	0.00
	5	0.00
2 mg./Kg. 180	1	0.00
	3	0.44
	5	4.00
4 mg./Kg. 90	1	4.00
	3	2.22
	5	0.00
4 mg./Kg. 180	1	2.22
	3	0.00
	5	1.33

Table 3

 W_4

Mean shock rates per hour for: (a) W_4 during the Methylphenidate Dose-Effect series on FI 180 LH 2; and (b) W_4 during the Reserpine-Methylphenidate series on FI 180 LH 2.

(a)

W_4		FI 180 LH 2
Control	1	2.13
	3	2.13
	5	1.46
1 mg./Kg. Methyl- phenidate	1	0.80
	3	0.53
	5	0.53
2 mg./Kg. Methyl- phenidate	1	1.06
	3	0.27
	5	1.06
4 mg./Kg. Methyl- phenidate	1	1.60
	3	2.93
	5	0.53

(b)

W_4		FI 180 LH 2
Pre- Reserpine Control	1	0.53
	3	1.06
	5	0.80
0.3 mg./Kg. Reserpine	1	2.80
	3	1.46
	5	1.86
0.3 mg./Kg. Reserpine; 2 mg./Kg. Methyl- phenidate	1	1.07
	3	0.53
	5	0.53
0.3 mg./Kg. Reserpine Only (a)	1	2.93
	3	0.27
	5	1.60
0.3 mg./Kg. Reserpine; 4 mg./Kg. Methyl- phenidate	1	0.53
	3	1.86
	5	2.93
0.3 mg./Kg. Reserpine Only (b)	1	1.86
	3	1.33
	5	0.53

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